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From Chairman's Desk

I am delighted to write for our journal which will be published again shortly, after several years due to Covid 19 and a number of unavoidable reasons.

However, after an initial month of restrictions in 2020, we commenced academic activities online, initially with series of webinars every month with topics on different specialties of internal medicine, Paediatrics and Obstetrics and Gynaecology. Subsequently we had many CMEs in person in several cities i.e. Kolkata, Mumbai, Siliguri. After a brief period, when examination was withheld during Covid 19, MRCPI Part I & II started again globally online 3 times a year. We sincerely hope to recommence clinical examination in India early next year.

In order to complete the publication soon, all members of the editorial team including the secretaries led by the Editor in Chief, Prof D.G. Jain have been working tirelessly.

I would like to extend my heartfelt thanks and gratitude to everyone involved for their sincere effort, assistance and cooperation.

With greetings of the festive seasons ahead and best wishes for the forthcoming year.

Dr. Sabyasachi Ray
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View Point

It gives me a sense of fulfillment to present you this issue of the JACI – Journal of Association of Clinicians of India with a pot pourri of rich clinical fare. Herein, I recall the famous words uttered by Socrates: "The only good is knowledge and the only evil is ignorance." And so it is!

Generally, the aims and objectives of all professional Associations are the dissemination of knowledge by way of Updates, Seminars, Symposia, Conferences and Journals. And ours is no exception. Over the last two decades, the Association of Clinicians of India has had the privilege of collaborating with the Royal College of Physicians of Ireland (RCPI) – till recently as a Chapter of the RCPI in India – in conducting online classes and hands-on clinical training programmes for the prospective MRCPI candidates as well as organizing the MRCPI Written and Clinical examinations for and on behalf of the RCPI in India.

Today we are in the midst of a mind-boggling age of unending information, knowledge, and technological ferment – DNA repair, gene editing, designer pills, immunologicals, targeted cancer therapies, robotic surgeries, and what-have-you! Therefore, Associations like ours – for the dissemination of updated, state-of-the-art medical research, clinical skills and technologies – serve the internists well.

In medical school, we were often told that if we sat alone in our room and read a topic, we would not understand or retain it as well as we would if we discussed it with our fellow students and colleagues. In the Indian medical curriculum, the post-graduate activity of a weekly journal club – a platform where original articles and case reports from current journals are discussed – serves as a training ground not only for conducting future clinical research independently, but also for preparing scientific papers suitable for publication and for presentation in conferences. Discussion and deliberation is, undoubtedly, the key to success in the field of medicine or for that matter in any field. We must not forget that after graduation there is no 'one' teacher. Our day-to-day teachers are the consultant-colleagues, contemporaries, and seniors with whom we interact – but most importantly, the patients whose complaints and agonies spur us to offer them safe and appropriate remedies culled from textbooks, journals, and enriching discussions with our team mates and consultants from other departments.

The onset of the Covid-19 pandemic also witnessed the onset and 'onslaught' of webinars – a novel approach which even the ACI had adopted successfully. The webinar served its purpose well as a safe platform during the pandemic; however, the enthusiasm of webinars gradually culminated in fatigue – reflected by the dwindling attendance. In this context, my lament is that nowadays there are far too many clinical meetings, seminars, symposia, conferences and webinars. As a physician, I feel it is neither practical nor healthy, or even necessary to participate in, or attend many of these. Attending or organizing conferences or webinars is not a race that we have to win. More often than not, an excess of such events ultimately eat into our personal

space and time and in effect erode our mental and physical well-being. Hence, we need to reflect deeply about our personal life – which most of us have neglected in more ways than one. How? We have not abided by the unwritten laws of nature which even the animal and plant world follow: Sleep on time, eat on time, and maintain a work-play balance. This is especially true for a majority of our medical professionals. You may have noted that in the West, the USA, and many other countries, doctors – like everyone else – do all the household work themselves and still manage to participate in academic and clinical events regularly. As you may be aware, the work culture in India and the Western world is entirely different. Abroad, the balance between work and personal life is a well-guarded culture. Clinicians are allowed to see only a limited number of patients in a day. Weekends are completely off. No patient can call you directly on the phone. It is indeed a well-balanced and healthy work culture. Whereas here in India – though we are so inclined to follow Western/American medicine, guidelines, and research – we carelessly turn a blind eye to their healthy work culture. A change in our work culture may not be appreciated by the Indian society where medical services and professionals are taken for granted and their services come under the ambit of the draconian Consumer Protection Act (CPA). All medical Associations would do well to chip in their bit by becoming platforms for the well-being of their own fraternity.

Decades ago someone had very rightly said: "The first wealth is health". In this context, I am reminded of my late father Dr. G. B. Jain – a Cardiologist and Fellow of the RCP, Edinburgh: Whenever he used to see me extra-busy, he would call me to his room and say, "Look son, take some time off. Skip your evening clinic… because life will end, but work will not. Spend some quality time with family and friends. Go out somewhere. Learn to relax… ." Since I have been following his sane advice religiously, I am tempted to pass it on to you as well! Therefore, time now for some out-of-the-box thinking. Time now to reflect and relook at our weekday and weekend routine. Time now to reboot, rejuvenate, and refresh.

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CONTENTS

BEDSIDE MEDICINE

Quo Vadis Clinical Medicine?

Kanjaksha Ghosh

Abstract

Medical teachers and educators lament on the ever decreasing clinical skills and history taking ability of current medical students across the world. This has been an universal finding across the globe. While the detailed reasons for such occurrence may vary from country to country, the paucity of good teachers, pressure of work, demand for quick diagnosis and treatment from patients and tremendous progress in investigative technology has resulted in loss of interest and love for both teaching and learning.

In spite of scientific advances medical teaching has a large body of experiential content with local flavour. Good teachers often used to combine these skills along with certain heuristics to develop quick understanding of the disease and reach a diagnosis. This needs to be learned with understanding of its pitfalls. Newer technology should improve our clinical skills, should spawn research in this area leading to development of better understanding in history and clinical diagnosis in the form of pathobiology and should help in formulating early diagnosis.

Key words

Medical Education, Clinical skills, History taking, Pathways to diagnosis, Heuristics, Pitfalls, Artificial Intelligence, Research on Clinical skills, bring back love for teaching and learning.

Introduction

A good four-to-five decades back when many sophisticated imaging and non imaging investigations as are used today were not available, our professors used to stress very much on good old clinical bedside medicine. With as many of the Oslerian adage they used to say without good bedside clinical medicine you, as a doctor is certainly to be doomed. Our professors of 1970s still believing in Oslerian dictum were great clinicians and they tried to inculcate that in our mind from the third year of medical school onwards to the end of our postgraduate course.

Bedside manners and ethics were simultaneously taught.

I have written about medical/clinical teaching elsewhere and side by side described some of the great all time medical teachers across the world to give a better perspective[1].

After we reached our first clinical bedside teaching in the 3rd year MBBS curricula (now the whole pattern has changed I gather) our Professor of Medicine an erudite Dr Jnan Mandal asked us the same question as our anatomy professor asked us 2 years back! Who will teach you clinical medicine? We replied at it should be yourself and many other teachers in the department. Prof. Mandal did not buy our view and gave us the same answer as our anatomy professor gave two years back for anatomy teaching (i.e., it is the dead body who will be your teacher and have respect for them). Only in this case it was the patients that would be our teachers.

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Who teaches you Medicine?

Our professor said: "Your patients will be your teachers. They will give you the diagnosis in the form of history, they will kindly allow you to examine them from head to foot applying all your senses and allow you to use some simple instruments bed side. Hence your job will be to hone your ability to take proper history in a reasonable time without offending the patient. You should be able from the given history-to separate the wheat from the chaff; and at the end of the history taking you should have reached three to five differential diagnoses ranked in the order of your priority. Thereafter you should complete your subsequent, clinical examination, condense your differential diagnosis and thank the patient again.

Now you plan the investigations to reach the diagnosis. Sometimes this is easy and at times it could be difficult. You should do to by a minimalist approach starting from the cheapest to the costliest, the less invasive to the more invasive for the diagnosis to be reached in the shortest possible time.

Some of these investigations which I call bedside investigations utilizing blood, urine. pus and other fluids obtained from the body —should be done at the side laboratory of your ward where you will have during many working hours. Technicians to help you, but at night and on holidays some of the investigations you have to do by yourself.

In case of an emergency some of these rules need to be broken. You may have to do costly and invasive investigation to save the patient in a situation when time is of essence."

Clinician's examination tool kit

Subsequently he gave us a list of simple instruments which ideally we should possess in our examination bag as follows :

1. A good quality stethoscope. 2.Two tuning forks-one with 128 Hz and the other with 512 Hz frequency to test vibration sense by Rinne Weber test for examining hearing faculty respectively. 3. A knee hammer to test tendon jerks. This hammer was often combined with an attached brush and a sharp end to test touch and sharp point discriminative touch. 4. A pin to test sharp sensation (should not be to sharp to so as cause injury) 5. A wisp of cotton to test for light touch 6. Two small tubes containing warm and cold water to test thermal sensation. 7. Two small bottles containing perfume to test for smell. 8. Salty, sour and sweet tastting substances in a solution for examining Taste sensation. 9. Tongue depressor or a wooden disposable spatula. 10. A measuring tape. 11. Otoscope 12. Ophthalmoscope. 13. An opaque 12 inch hollow cylinder (often we used to make it from used X-ray plates) for doing transillumination test. 14. A pair of gloves and two finger latex stalls to do internal examination. 15. Snellen's Chart, near reading chart for testing visual acuity, few Ishihara isochromatic figures to test color blindness. 16. A white paper to test writing (often useful for liver disease, Parkinsonism, etc.) 17. Additional tools like weighing machine Sphygmomanometer, anoscope, vaginal speculum, indirect laryngoscope etc., used to be available at the ward with the on duty nursing staff.

Those who are of my age or older can judge how many of them we really carried in our clinical examination bag, but now and then we felt we should have carried them. I will come back to this list again referring to it in a later section of my writing.

Contribution of History taking in final diagnosis

Very often it has been asked, particularly as we advanced in the field of imaging and other laboratory technology to pick up many disorders in the early stages as to why we should emphasise so much on history taking? Since 1975 this question is being asked and the answer surprised us, and it will surprise readers as well: A good history contributes 75-76% of clinical diagnosis, clinical examination contributes another 15 per cent, and the rest is contributed by our all powerful imaging and other diagnostic technology[2,3]. I have been trying to develop my own best way to take a medical history almost all my life, and I believe every doctor continues to develop his/her own way to take a history. The idea is to develop a style that is brief but sufficiently informative to reach the heart of the problem i.e., 'the diagnosis'. In our early clinical years we used to elicit a lot of history, a large part of which was not of much use. Although all over the world the framework of eliciting the clinical history is similar, i.e., it progresses through:

i. Chief complaint and its evolution to the present history ii. Past medical history iii. Family history. iv. Present and past drug histories, allergies, idiosyncrasies, etc. In our student days, history used to be huge and as we neither had the requisite experience or the theoretical knowledge about various common disorders. Often our history used to take us nowhere till we faced what is called supervised history taking. Here a teacher used to guide us through the morass of information we collected as history. Though it was said history is to be taken in the patient's own words without complicating with the lingo of medical conditions, nowadays this is hardly possible.

Uninterrupted history taking is ideal but guidance to patients is often necessary and here the supervisor's skills clearly show. It has now been established supervision along with a detailed history taken by his juniors provide the best diagnostic data[4].

After history taking is over, clinical examination had to be learned as an art without inconveniencing the patient. Head to toe could be examined at a single swipe like a maestro in a symphony. Some of our professors were masters at that. It was a pleasure to see them in action and emulate them in our practice. At the end of history taking and during clinical examination additional points could be cleared through further exploration in history and a differential diagnosis and a list of investigations required to reach final diagnosis used to be made.

There is no denying that clinical skills like taking a good history may take years to learn well. The pathways to the various investigations were made in the way already described.

Methods of diagnosis

Questions arise as to how we make a diagnosis[5] using history, clinical examination and investigations, as each of them standing alone is not infallible.

i. Representative pattern recognition: As we get more experienced and know more about the disease we could quickly recognize a pattern to make the diagnosis, just like we don't take even a moment to identify a familiar face.

ii. Reasoning: For each of the points in the history, clinical examination and investigations, we reason out to make a comprehensive story which dazzles with simplicity and one diagnosis (Occam's Razor concept).

iii. Suspecting and Excluding: From the list of differential diagnosis we suspect and reject, based on available evidence.

iv. Follow up: Many-a-times for a disease in evolution particularly a chronic disease, it may not be apparent in the beginning, the real nature of the disease, which can be clarified only in in subsequent follow-ups.

v. Diagnosing by probability: During an epidemic, a disease with similar history and presentation is likely to be diagnosed as that causing epidemic itself. A shadow in the right upper lobe of the lung or a clinical presentation directed at that area with low grade fever and weight loss in India is likely to be diagnosed as pulmonary TB and not as Coccidiodomycosis/Psittacosis/Histoplasmosis.

This method today has mathematically progressed to Bayesian decision analysis[6] through the following steps:

(a) Identifying the decision problem.

(b) Structuring the decision problem over time.

(c) Measuring the uncertainties (probabilities and utilities in the structure).

(d) Combine the uncertainties for developing a diagnosis or preferred course of action.

vi. Diagnosing by iteration and reiteration: One goes back and forth to the history and clinical examination again and again to pick up important lost threads that give away the diagnosis.

One of my favourite professor used to profitably use this technique in difficult to diagnose hospitalized patients. One has seen a patient admitted for weeks without diagnosis, his/her case file gaining in girth and nobody now goes deep into the patient's problem.

He used to technically readmit such a patient. He would assign a postgraduate trainee, (taking away all the files) to take an in-depth of the history and exploring unexplored areas-if needed by going to the library. The junior doctor had to formulate his/her differential diagnosis for presentation to the professor. Occasionally such an act has given a good insight combining the presentation of the

case, progress in the hospital, effect of various interventions and follow-up investigations to finally help build a picture recognizable in a clinical pattern.

vi. Putting thoughts of several clinicians with different experience together, i.e., setting up a medical board.

Here a group of clinicians (in a similar way could be students) discuss the clinical challenge and with their different experiences and skill sets contribute to the diagnosis.

Fallacies in clinical diagnosis

An experienced teacher of medicine uses all of the above methods by combining them in his mind, but more often he/she uses heuristics, a cognitive short cut, which are simple decision strategies ignoring a part of the available information. They base their decisions on only a few relevant predictors. Heuristics may outperform information-greedy methods, such as regressions in medical diagnosis[8,9].

As heuristics are cognitive shortcuts to diagnosis. They may fail on, in certain occasions, when a particular case appears to be representative of the class, but is not, like phenocopies of a genetic condition or a new disease. Not infrequently, the cognitive short cut is restricted by availability of the pattern to the diagnostician i.e., limited by experience, remembering easily the most recently seen case. Simplicity in a single diagnosis (Occam's razor) may not be true as in some cases two or more different condition may be present (Hiccam's dictum) in the same patient—not an unusual occurrence in an ageing population. One should be careful about thinking of two different diseases in one patient. It is believed that an intelligent mind can conjure multiple conditions by combining an array of symptoms (Crabtrees Gabtree's Warning) The old adage that a rare presentation of a common condition is more common than a common presentation of a rare condition comes to mind. iv. Another drawback is the tendency to anchor one's diagnosis and then search for supportive evidences neglecting a load of opposing evidences to stick to a diagnosis[5,10].

Clinical Medicine in the current era

Which way is the clinical medicine is going now? It is not very easy to answer it in a few simple sentences. It is seen that with the explosion of imaging techniques and laboratory medicine, doctors are relying less on detailed clinical history taking and extensive clinical examination of the patient. So without relying mostly on the various diagnostic modalities as has been already described, a clinician is now having at hand an extensive array of reports with only a brief clinical history of the patient. This saves the time of both the clinician and the patient presumably.

However, the basics of clinical medicine still continue to be taught in medical colleges. In the process, patients have lost the touch and more extended interaction with their doctor. Now we don't hear, "Listen carefully to the patient, he is giving the diagnosis". Clinical skills of recently graduated students are also becoming inadequate[11,12]. Moreover students are required to cope with increasing number of issues and subjects in their shortened medical curricula. Medical research which, at least in India, was never seriously considered and taught in undergraduate and even in post graduate curricula is increasingly getting prominence without proper ground work being done[13,14]. Research is equally applicable in day to day practice and in clinical medicine. The findings may contribute local knowledge of disease prevalence, antibiotic resistance, etc. This knowledge may also help local and national authorities to modify or formulate various national health strategies and programmes. Occasionally some new diagnostic information or test may be developed and this may have an international value also and show how a simple clinical observation may still be relevant to develop a new clinical test[15].

In recent years, several new tools have joined our clinical examination armamentarium e.g., i. Pulse Oximeter to measure peripheral oxygen saturation which can be related to arterial oxygen tension through a suitable nomogram. Nowadays doctors carry a Pulse Oximeter in this post-Covid era. ii. Finger prick testing for blood glucose. iii. Hand held mobile connected ECG machine with software to read common cardiac conditions. iv. Hand held USG machine and blue tooth stethoscope (to avoid physical patient contact), to name a few. Proper place of these machines in

day-to-day clinical examination and diagnosis has not yet been fully explored and when this data is connected with the power of artificial intelligence the capability of a lone doctor on an emergency call at night will be immensely increased.

Now-a-days artificial intelligence has appeared on the scene to assist us in almost every respect like taking history, giving differential diagnosis, suggesting and reporting investigation results[16]. In future years this is expected to get even better. With the advent of such AI tools will our medical education be compromised or will it be enhanced? Only time will tell.

Paucity of good teachers, pressure of administrative and other work, tremendous increase in the information to be learned, pressure from the patients for quick diagnosis and management have contributed to the loss of interest and love for teaching as well as learning at the bedside. In addition many learning tools through the internet based system are now available.

Discussion

Undeniably many medical educators across the world and also in India lamented on the quality of history taking and clinical skills of recently qualified medical graduates. The reasons for such a finding could be different in different parts of the world. What is important is that both the teachers and the taught are not finding pleasure in teaching and learning, i.e., what has been described, the love to teach and the love and surprises to learn new things have essentially vanished[17].

This needs to be back in the medical schools and the patient's bedside.

We must give up the idea that imaging and laboratory investigations will find the diagnosis for us rather than having the joy of picking up new points in the clinical history and physical examination. Iterative discussion and formulating the differential diagnosis and later finding how closely this diagnosis has been supported or refuted by the investigative results of imaging, do copy/ laboratory results should be the norm. Many of us no longer need to go to side laboratories of the hospital wards (such laboratories have nearly vanished and no longer exists in most of the medical colleges) to learn first hand with the help of simple investigations on peripheral blood smear, stool, urine, and examination of other secretions/ excretions, etc.

In fact, all the modern accessories of medicine rather than making us lose what our great clinical masters have taught us can enable us to really build on it. There will still be pleasure in hearing hums of the heart, rubs of the pleura/pericardium, splash of succession in different diseases! Various laboratory investigations and imaging may pick up both abnormal results in healthy people (irrelevant white spots of MRI scans!) and abnormal results as an early evolution in the disease. Repeated history taking and clinical examination may unravel newer clinical signs and symptoms enriching clinical medicine.

The way we assess the clinical skills and diagnostic ability of students by examination has substantially changed, often replacing real patients with clinical vignettes and physical examination results in the form of Objectively Structured Clinical Examination (OSCE). This type of examination has been considered more objective, capable of examining a candidate at any particular depth and does not need the real patient to be present. The pros and cons of these types of examinations has recently been discussed and loss of various skills as one faces the real world patients has been described[18]. Similarly with the advent of AI (Artificial Intelligence) in many of its facets, a virtual patient may be created. So also, the virtual physical examination and clinical history taking may be emulated. Again, how this will fit in in the medical education of today in improving one's clinical skill needs to be seen. We must always keep at the back of our mind that a map is not the actual territory. One needs skills to read a map, but may also need a higher levels of skill and experience to negotiate a territory mapped in the map!

The new instruments like point of care ECG, Pulse Oximeter and Point of care ultrasound (POCUS)[19], needs extensive field testing and orientation of the future generation of doctors to be able to use them profitably for their day to day use. Finger prick blood glucose monitors have already established their role in bedside diagnostics. However, I believe it is still not extensively used by the students, residents, as well as the practicing doctors.

Every generation laments that the generation next seems to be lacking in the skills/mental concentration abilities of the previous generation; this has recently been analysed and contested[20]. Each generation does learn many new skills as the way we live changes. These new skills should be integrated meaningfully to foster a new era in clinical medicine.

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REVIEW ARTICLE

Renal Artery Stenosis: The Problem and the Solution

Prakas Chandra Mondal[1], Indrajit Debnath[2]

Abstract

Renal artery stenosis (RAS) is a major cause of renovascular hypertension. While atherosclerosis and fibromuscular dysplasia being the most common causes worldwide in older and younger patients respectively, Takayasu arteritis is more common in young Indians. Renin-angiotensin-aldosterone system (RAAS) plays the central and key role in the pathogenesis of RAS. Clinical presentation may vary from asymptomatic radiological abnormality to renovascular hypertension which may progress and complicate to end-stage renal disease. While initial evaluation with less invasive tests such as ultrasound, duplex ultrasound, CT and MR angiography are being employed, invasive renal angiography remains the gold standard investigation. Conservative management with antihypertensive agents may slow the disease progression, statin slows lesion progression, reduced restenosis risk after renal stenting and are associated with improved survival. Revascularization in the form of percutaneous or surgical revascularization is reserved for patients with haemodynamically significant RAS with some particular aetiology or with some clinical scenarios.

Keywords

Renal artery stenosis, renovascular hypertension, renal angiography, fibromuscular dysplasia, revascularization

Introduction

Renal artery stenosis (RAS) is narrowing of one or both of the renal arteries. It is the major cause of renovascular hypertension and accounts for 1% to 10% of the 50 million cases of hypertension in the United States[1]. Other than renovascular hypertension, renal artery stenosis may progress and complicate to chronic kidney disease and end-stage renal disease[2].

Aetiopathogenesis

Atherosclerosis is the most common cause of RAS worldwide in older (men over the age of 45 years) patients.

Among the younger patients (often affects women in the age group 30-50 years) fibromuscular dysplasia is the most common cause worldwide, while Takayasu arteritis is more common in younger Indians[3].

Other less common causes include thromboembolic disease, arterial dissection, infrarenal aortic aneurysm, vasculitis (Buerger's disease, polyarteritis nodosa, post-radiation), neurofibromatosis type 1, retroperitoneal fibrosis.

Atherosclerotic Renal Artery Stenosis

(ARAS) is predominantly seen in older patients as a part of systemic atherosclerosis and is mostly bilateral and present as eccentric or concentric lesions located approximately 1 cm from the

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ostium or in the proximal one-third of the renal artery. Atherosclerotic changes in the renal vessels often cause total obstruction of the renal artery and subsequently ischaemic atrophy of the affected kidney[4]. Patients often have the characteristic risk factors: diabetes, hypertension, dyslipidaemia, smoking history, peripheral vascular disease, and coronary syndromes[4,5]. Moreover, some genetic predisposition to the development of ARAS has also been demonstrated, e.g., a significantly higher frequency of the angiotensin-converting enzyme (ACE) gene ACE-D allele when compared to matched control subjects was demonstrated in ARAS patients[6].

Fibromuscular Dysplasia

(FMD) is a non-inflammatory and non-atherosclerotic malformation of the vasculature which may affect various arteries including carotid or vertebral arteries apart from renal artery[7,8,9]. Anatomically, and according to angiographic appearance, FMD occurs in three types: medial (85–90% of all FMD cases), intimal, and adventitial or periarterial[5,8,9]. FMD may lead to arterial stenosis, aneurysm formation with dissection of medium-sized vessels. Unlike ARAS, FMD rarely causes total occlusion and severe ischaemic complications[5]. FMD most often affects women between 30–50 years of age and typically involves the middle and distal main renal artery or the intrarenal branches[7]. This typical age group suggests that hormonal influences may be essential in FMD pathophysiology. However, it is not fully understood, and different aspects, including smoking, family prevalence of some diseases (phaeochromocytoma, Ehler's-Danlos syndrome type IV, Alport's syndrome, cystic medial necrosis, coarctation of the aorta), a genetic predisposition has also been suggested[5,8,9].

Pathophysiology of Renovascular Hypertension and Ischaemic Nephropathy

Renal artery stenosis (RAS) is characterized by the progressive narrowing of the large and medium-sized renal arteries[7]. Kidneys are relatively over perfused organs when referring to metabolic requirements as studies have demonstrated that only about 10% of the oxygen contained in the blood of a perfusing kidney is necessary to maintain the energy demand of this organ[10,11]. Thus in a patient with a moderate renal blood flow (RBF) reduction may be sufficient to disturb glomerular filtration rate (GFR) and renal autoregulation of RBF, which results in invariable activation of renin–angiotensin–aldosterone system (RAAS) activity, while maintaining oxygen supply to both the cortex and the medulla of the stenotic kidney without the inevitable threat to the viability of the kidney tissue[10,12]. Therefore, the term "azotemic renovascular disease" is proposed by some authors as a more adequate term compared to the commonly used "ischaemic nephropathy" for the description of such an entity[13]. It is important to draw attention to the fact that RAS is not a simple synonym for RVH, rather RAS is an anatomical diagnosis and often considered clinically significant when there is a $\geq 75\%$ narrowing of the diameter of a main renal artery or $> 50\%$ luminal narrowing with a post-stenotic dilatation, and many lesions identified with imaging studies, mostly in elderly patients, remain clinically insignificant[7,14].

Activation of RAAS activity results in release of renin from renal juxtaglomerular cells, which acts on its substrate angiotensinogen to produce angiotensin I which in turn is transformed by angiotensin-converting enzyme (ACE) into angiotensin II in the pulmonary capillary bed. Angiotensin II is a potent vasoconstrictor per se, and promotes the release of aldosterone from the adrenal cortex which causes retention of salt and water, thus resulting in secondary hypertension or renovascular hypertension[15]. The more severe and prolonged diminishing of RBF may threaten the oxygen supply to the organ, eventually leading to kidney fibrosis and remodelling of the kidney structure resulting from action of the key compound, angiotensin II, which also exerts strong profibrotic effects, and many other inflammatory mediators like TGF-β, TNF-α, MCP-1, etc. Since these pathways are a part of the complex pathophysiology of atherosclerosis, kidney fibrosis, ischaemic nephropathy and eventually chronic kidney disease mostly develop in ARAS patients, and is rarely observed in those with fibromuscular fibrosis[10].

Clinical Presentation

Clinical manifestations suggesting the diagnosis of renovascular hypertension as a cause of hypertension include:

- Abrupt onset of hypertension in young patients (30–50 years of age) suggestive of FMD; and after about 50 years of age; suggestive of ARAS.
- Young-onset hypertension with negative family history.
- Acceleration of previously well-controlled hypertension, refractory to therapy with three or more anti-hypertensive drugs.
- Features of malignant hypertension.
- Unexplained and unprovoked acute kidney injury.
- Unexplained rise in BUN, unexplained hypokalemia.
- Acute kidney injury following the administration of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).
- Unilateral small kidney (asymmetric kidneys with more than 1.5 cm of difference in the size).
- Recurrent episodes of flash pulmonary edema and/or refractory heart failure.

Other Findings

- Continuous, high-pitched holosystolic with diastolic component abdominal bruit or flank bruit.
- Severe retinopathy.
- Carotid, coronary or peripheral vascular disease (suggestive of ARAS)[16].

Evaluation

The gold standard for diagnosing renal artery stenosis is renal angiography. As the technique is invasive, a variety of less invasive tests are being employed for initial evaluation of RAS[17,18]. However, if the non-invasive test is inconclusive and the clinical suspicion remains high, conventional renal angiography is recommended.

Laboratory Studies

- Serum creatinine levels to assess the degree of renal dysfunction.
- Urine analysis -
- A 24-hour urine for protein, or a protein-creatinine ratio on a random void urine specimen, to assess the level of renal dysfunction and the degree of proteinuria. The renal vascular disease is more often associated with minimal-to-moderate degrees of proteinuria, non-nephrotic range.
- Red blood cells or red blood cell casts are absent
- Serological tests - e.g., antinuclear antibodies, C3, C4, antinuclear cytoplasmic antibodies for systemic lupus erythematosus (SLE) or vasculitis, if these conditions are suggested.

Imaging Studies

Imaging studies for the renovascular disease are warranted for those who fulfil the following criteria:

- The clinical findings suggest the cause of hypertension as secondary rather than primary.
- Exclusion of other causes of secondary hypertension such as primary kidney disease, primary aldosteronism, or phaeochromocytoma before investigating for renal artery stenosis.

Ultrasonography

The contribution of ultrasonography scanning to the entity of renal artery stenosis is a suggestion of the diagnosis when examination results indicate significant asymmetry of kidney size (i.e., size discrepancy of >1.5 cm). Ultrasonography may also be useful in detecting the presence of a solitary kidney, in which case, renal artery stenosis of that solitary kidney takes on more significant prognostic and therapeutic importance.

Duplex Doppler Ultrasonography

Duplex ultrasonographic scanning is a non-invasive technique, which combines direct visualization of renal arteries with Doppler velocity measurements of blood flow and is an excellent screening test for RAS[19] that can be used in patients with any level of renal function.

A. Direct Visualization of the Renal Arteries

This involves direct scanning of the main renal arteries with color or power Doppler ultrasound followed by spectral analysis of renal artery flow. Signal enhancement can be achieved by administering contrast agents that facilitate

visualization of the renal arteries. Four criteria are currently used to diagnose significant proximal stenosis[20,21,22]:

1. An increase in peak systolic velocity in the renal artery (the post-stenotic threshold for significant RAS is 100 cm/sec to 200 cm/sec is reported).
2. A renal-to-aortic peak systolic velocity ratio of greater than 3.5.
3. Turbulent post-stenotic site.
4. Visualization of the renal artery without any detectable Doppler signal, an observation that signals occlusion.

B. Analysis of Intra-renal Doppler Waveforms

The different segments of kidneys are scanned via trans lumbar approach systematically to detect a stenosis of a segmental or accessory renal artery. Quantitative criteria proposed for detection of significant RAS:

1. Acceleration of less than 370 cm/sec to 470 cm/sec. The early systolic acceleration seems to be the best predictor of renal artery narrowing.
2. Acceleration time greater than 0.05 sec to 0.08 sec.
3. Change in the resistive index (RI) of greater than 5% between the right and left kidneys.
4. A dampened presentation (pulsus tardus) of an intrarenal Doppler waveform indicates stenosis.
5. The presence of an early systolic peak can be interpreted as a sign of normality; however, the absence of an early systolic peak is not necessarily indicative of stenosis[23].

CT Angiography

CT angiography uses an intravenous injection of a relatively large dose of iodinated contrast and allows 3-dimensional reconstruction images visualizing the whole vasculature including the presence of accessory renal arteries. But it has associated risk of contrast associated nephropathy, particularly in patients with pre-existing chronic kidney disease.

MR Angiography

Magnetic resonance angiography (MRA) is a non-invasive technique and different imaging methods can be used:

- Time of flight (TOF) in which the high velocity of the blood jet at the level of stenosis appears as signal void or simply black.
- Phase contrast technique.
- Gadolinium-enhanced MR angiography: Usually, a double dose of gadolinium contrast material (0.2 mmol/kg) is injected at a rate of 1.5–2 mL/sec. Blood is rendered bright, whereas stationary tissues remain dark. Subtraction of nonenhanced images removes all background signals and improves the vessel-to-background signal.

According to several case studies, MRA has been justified only for diagnosing stenosis situated in the proximal 3 cm to 3.5 cm[24].

Conventional Arteriography

As mentioned initially conventional angiography remains the diagnostic gold standard for the identification of RAS. Renal arteriography can be performed by several methods including conventional aortography, intravenous subtraction angiography, intra-arterial subtraction angiography, or carbon dioxide angiography.

Conventional aortography produces excellent radiographic images of the renal artery. This technique requires an arterial puncture, carries the risk of thromboembolism, and uses a moderate amount of contrast with the risk of contrast-induced acute tubular necrosis. Low-osmolar contrast material can reduce this risk.

Intravenous subtraction angiography is sensitive for identifying stenosis of the main renal artery but not accessory or branch renal arteries sufficiently. This method avoids the use of a high volume of contrast, the risk of arterial puncture and thromboembolism.

Intra-arterial digital subtraction angiographic technique has a high diagnostic accuracy compared to conventional angiography and are associated with fewer complications due to the lower dose of contrast, and smaller catheter size used.

Carbon dioxide angiography is an alternative angiographic contrast agent used in combination with digital subtraction angiography to avoid the risk of conventional nephrotoxic contrast agents in patients with severe renal disease; however, the technique requires an experienced investigator and a dedicated person to inject the carbon dioxide.

Treatment

Medical Therapy

Antihypertensive drugs (ACEIs, ARBs, calcium channel blockers, beta-blockers and diuretics) are effective for treating hypertension and may lead to slowing of the progression of renal disease[25,26]. ACEIs and ARBs have shown benefits in reducing mortality and morbidity in patients with renal artery disease. Optimal blood pressure (BP) in the setting of renal artery disease is unknown and it has been hypothesized that severe RAS might require higher BP to maintain adequate blood flow across the stenosis. Patients with bilateral severe RAS or RAS in a single functional kidney require very careful monitoring when started on ACE inhibitors or ARBs[27].

Statins slow lesion progression, reduced restenosis risk after renal stenting and are associated with improved survival[28,29]. Antiplatelet therapy should be part of best medical therapy (BMT)[27].

Revascularization

The American College of Cardiology and the American Heart Association (ACC/AHA) guidelines recommend percutaneous revascularization in patients with haemodynamically significant RAS and any of the following particular aetiology or clinical scenarios[30]:

- Recurrent congestive heart failure or sudden unexplained pulmonary oedema (Class I)
- Unstable angina (Class IIa)
- Accelerated, resistant, or malignant hypertension or hypertension with unexplained unilateral small kidney and intolerance to medication (Class IIa)
- Asymptomatic bilateral or single functioning kidney; however, this treatment is clinically unproven in asymptomatic unilateral haemodynamically significant RAS in a viable kidney (Class IIb)

ACC/AHA gives a class I recommendation for renal stent placement for ostial atherosclerotic RAS and also balloon angioplasty with bailout stent placement if necessary for fibromuscular dysplasia lesions[30].

For surgical revascularization, ACC/AHA gives class I recommendations for the following indications[30]:

- Fibromuscular dysplasia, especially in those exhibiting complex disease or macroaneurysms.
- Atherosclerotic RAS and multiple small renal arteries or early primary branching of the main renal artery.
- Atherosclerotic RAS in combination with pararenal aortic reconstruction.

Conclusion

Patients with renal artery stenosis represent a diverse group which vary from asymptomatic radiological abnormality to renovascular hypertension which may progress and complicate to end-stage renal disease. The initial evaluation should be with renal ultrasound, duplex Doppler ultrasound, but invasive renal angiography remains the gold standard investigation. Management primarily consists of antihypertensive agents and statins which may slow the disease progression and are associated with improved survival. Revascularization in the form of percutaneous or surgical revascularization is reserved for patients with haemodynamically significant RAS with some particular aetiology or clinical scenarios.

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Renal Replacement Therapy : How To Do It

Ranajit Chatterjee (Chattopadhyay)

Introduction

One of the most rapidly developing specialties in medical science is Critical Care Medicine. The lastfew decades have witnessed a tremendous advancement in the field of technology, diagnostics, and treatment of critically ill patients. One such technological marvel is Renal Replacement Therapy (RRT). RRT is now routinely used in intensive care as a renal support and its use has been extended further beyond the boundaries of acute kidney injury in various clinical settings making it more of a supportive system for different organ systems involvement.

Types of therapies and their mechanism of action

RRT can broadly be divided into two types, continuous and intermittent therapies. The continuous therapies are Continuous Veno-Venous Haemodialysis (CVVHD), Continuous Veno-venous Haemofiltration (CVVHF) Continuous Veno venous Haemodiafiltration (CVVHDF) and Slow continuous Ultrafiltration (SCUF). The Intermittent therapies are Intermittent Haemodialysis (IHD), Sustained Low Efficiency Daily Dialysis (SLEDD) and Peritoneal Dialysis (PD). The role of intermittent therapies is limited in critically ill patients where the much slower continuous or extended therapies are preferred.

Mechanism of action

It is either diffusion or convection and ultrafiltration. Whereas diffusion is movement of small molecules against concentration gradient across a semipermeable membrane, convection does the same, but against a pressure gradient. It also drags a lot of water along with the solutes which is called solvent drag. This is the process of ultrafiltration. Convection also moves larger molecules as opposed to diffusion which only moves the smaller molecules. Thus, convection might benefit patients of sepsis where middle molecules are thought to be involved in its pathogenesis. It is also more physiological compared to diffusion as human kidneys work by the process of diffusion. Convection-based replacement techniques (haemofiltration and haemodiafiltration) using high-flux membrane-filters are aimed at maximizing the removal of the so-called medium and high-molecular weight solutes (higher than 1000 kDa up to several thousand kDa), as opposed to the so-called low-molecular weight toxins. Adsorption is the adherence of solutes to the membrane filter surface that leads to its removal from blood. Adsorption of solutes occurs to varying degrees in all CRRT circuits and can be a contributor for large-molecule removal, depending on membrane characteristics. This may be limited by saturation of the membrane binding sites that can occur within a few hours.

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The membranes

Used in CRRT are synthetic membranes which have large pores and huge adsorptive surface allowing a lot of bigger molecules to pass and also helping in adsorption of molecules. The newer membranes are also more biocompatible and chances of complement activation is minimal. There are different varieties of filters available in the market as per the weight of the patient and surface area of the membrane.

A good vascular access

Is essential for a successful RRT. Catheter has to be inserted under Ultrasound guidance in the following order of preference: **right internal jugular vein > right femoral vein**. The subclavian and left internal jugular vein vein has to be avoided. The right internal jugular gives the best result as there is a pool of blood in continuity with the right atrium which helps in a less resistant flow in the catheter. Length of insertion should be 15 cm for right internal jugular vein. If the femoral vein is to be selected, the catheter has to be introduced at least 20-24 cm in order to avoid recirculation inside the catheter. An intensivist with sufficient experience in placing catheters should place the catheter. The catheter should be soft, polyurethane, uncuffed. Tunnelling has no advantage over untunneled catheters. 11F catheter has a flow of 250-300 ml/min. Using a blood pump, the patient's blood is removed via the red coded line (Access) typically connected to the red port of the catheter and delivered through the haemofilter back to the patient via the blue coded line (Return) typically connected to the blue port.

Many-a-times in critically ill patients, the right internal jugular vein is occupied by a central line and by default the femoral line is chosen for RRT.

As a lot of fluid is removed by the process of ultrafiltration, it has to be replaced to the patient either fully (**zero balanced RRT**) or partially (**negative balanced RRT**). The **replacement fluid** nowadays is *bicarbonate based* and lacks potassium. Hypokalaemia is one of the complications of CRRT and potassium needs to be replaced either giving it separately or by adding potassium in the bag. The fluid can be replaced either before (**pre-filter**) or after **post-filter** the filter. Prefilter replacement compromises convection but prolongs filter life in contrast to post filter which does a perfect convection at the cost of filter life. The replacement fluid also needs to be altered during hypo and hypernatremia.

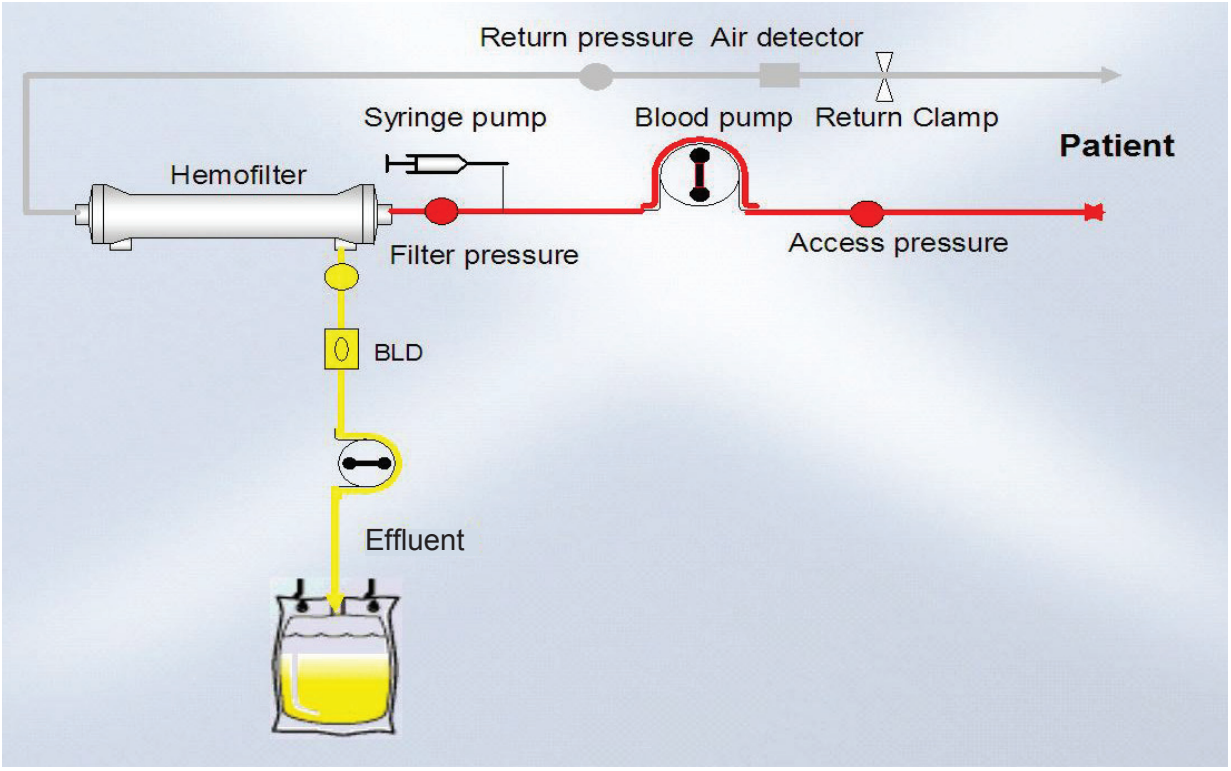

Fig. 1 Slow continuous ultrafiltration technique (SCUF)

CRRT Modalities (Based on principles)

1. Slow Continuous Ultrafiltration (SCUF)

Primary therapeutic goal: Safe management of extra fluid removal.

Primary indications:Fluid overload without significant electrolyte imbalance.

Principle used: Ultrafiltration.

Therapy characteristics: No dialysate or substitution solutions. Fluid removal only.

SCUF is a very useful modality in patients of diuretic resistant and haemodynamically unstable pulmonary oedema. It is also helpful in removing fluid in cases of cerebral oedema especially in a patient of acute liver failure and subsequent hepatic encephalopathy[1]. Figure 1 Demonstrates SCUF Technique.

2. Continuous Veno-Venous Haemofiltration (CVVH)

Primary therapeutic goal: Solute removal and safe management of fluid volume.

Primary indications: Uraemia, severe acid/base or electrolyte imbalance, when removal of larger molecular weight substances is required.

Principle used: Convection.

Therapy characteristics: Requires replacement solution to drive convection. No dialysate solution.

Effective at removing small and middle molecules. Figure 2 shows Continuous Veno-Venous haemofiltration technique

3. Continuous Veno-Venous Haemodialysis (CVVHD)

Primary therapeutic goal: Solute removal and safe management of fluid volume.

Primary indications: Uraemia, severe acid/base or electrolyte imbalance.

Principle used: Diffusion.

Therapy characteristics: Requires dialysate solution to drive diffusion. No replacement solution.

Effective at removing small molecules. Figure 3 Demonstrates the technique of Continuous Veno-Venous Hemodialysis (CVVHD).

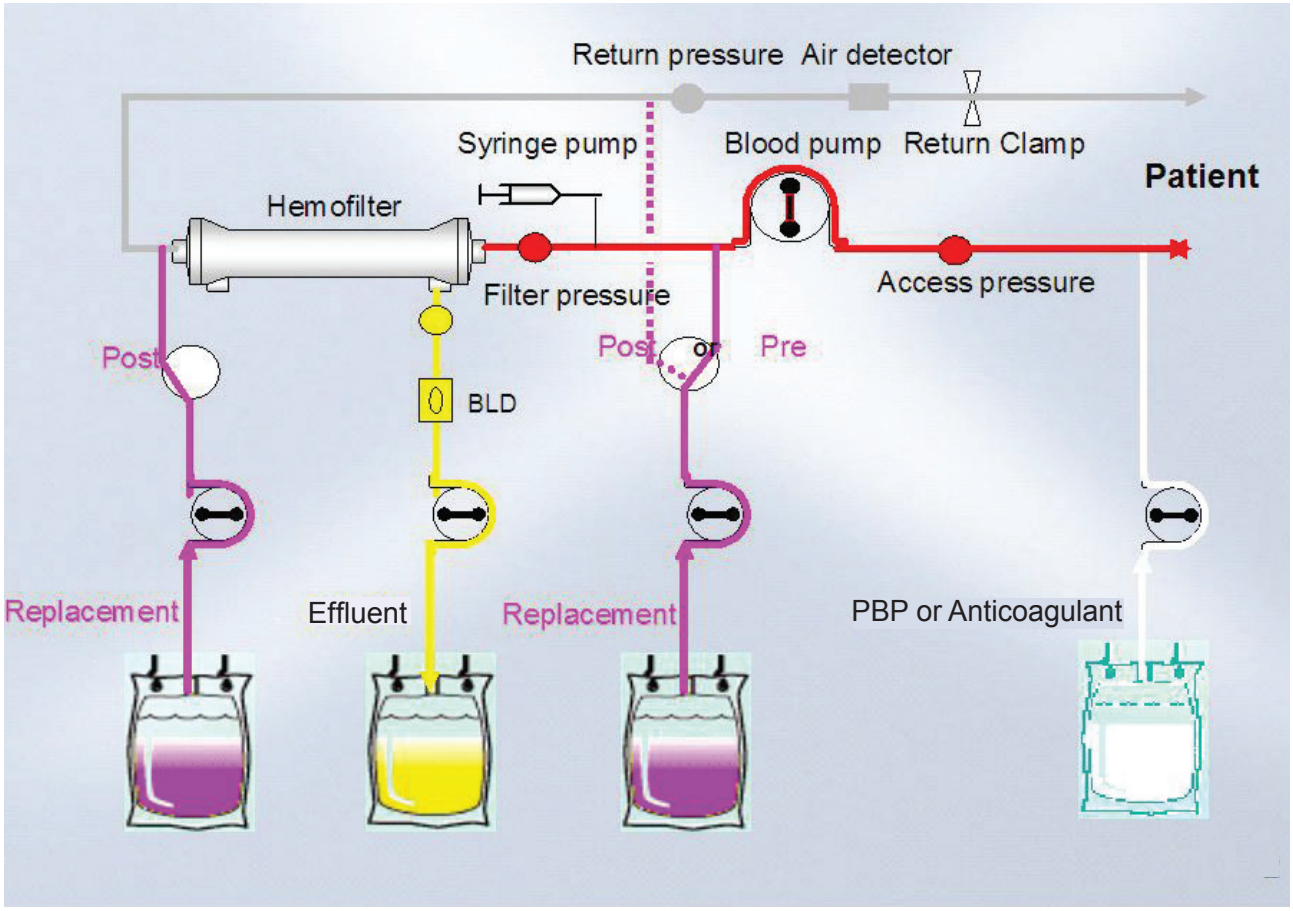

Fig. 2 Continuous veno-venous haemofiltration technique (CVVH)

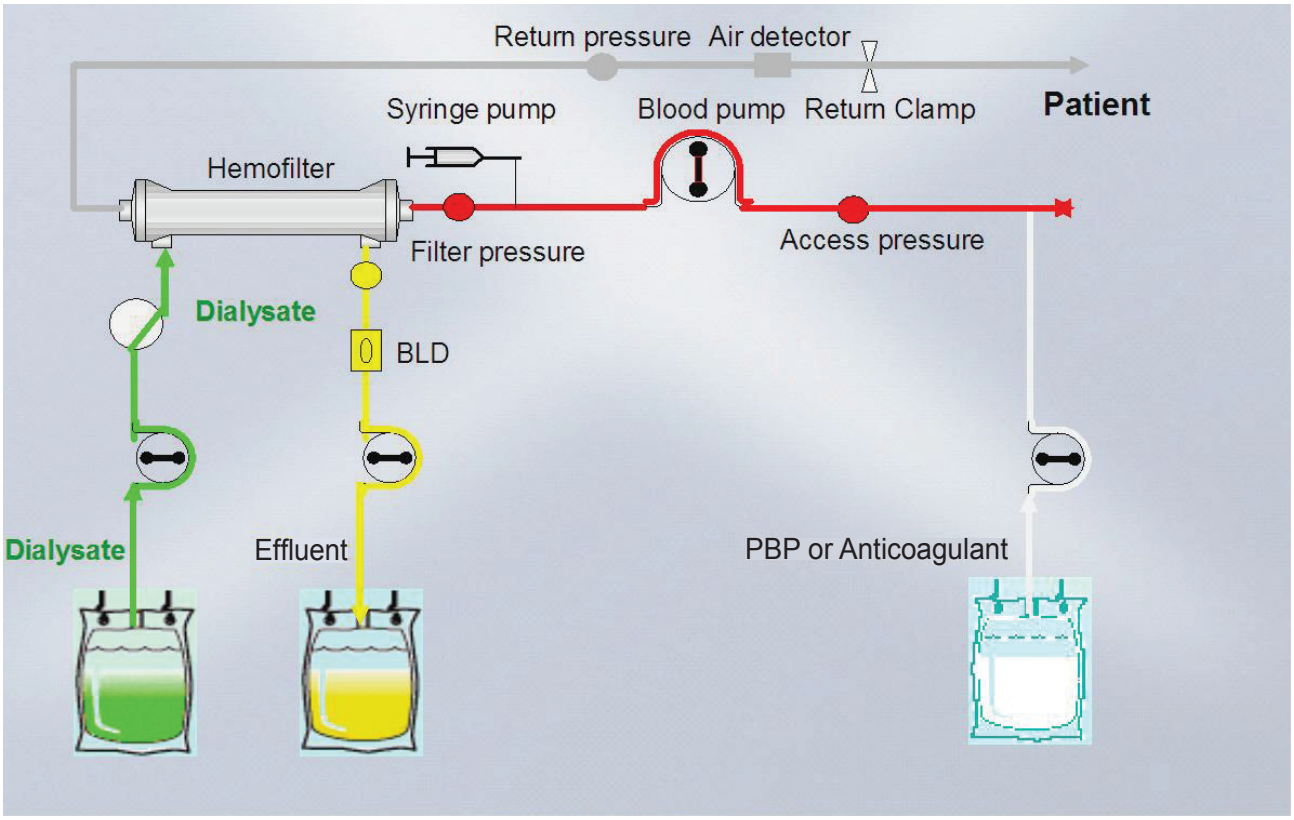

Fig. 3 Continuous Veno-Venous Haemodialysis (CVVHD) technique

4. Continuous Veno-Venous Haemodiafiltration (CVVHDF)

Primary therapeutic goal: Solute removal and safe management of fluid volume.

Primary indications: Uraemia, severe acid/base or electrolyte imbalance, when removal of large molecular weight substances is required.

Principle used: Diffusion and convection

Therapy characteristics: Requires dialysate fluid and replacement solution to drive diffusion and convection.

Effective at removing small, medium and large molecules. Figure 4 shows the technique of Continuous Veno-Venous Haemo Diafiltration.

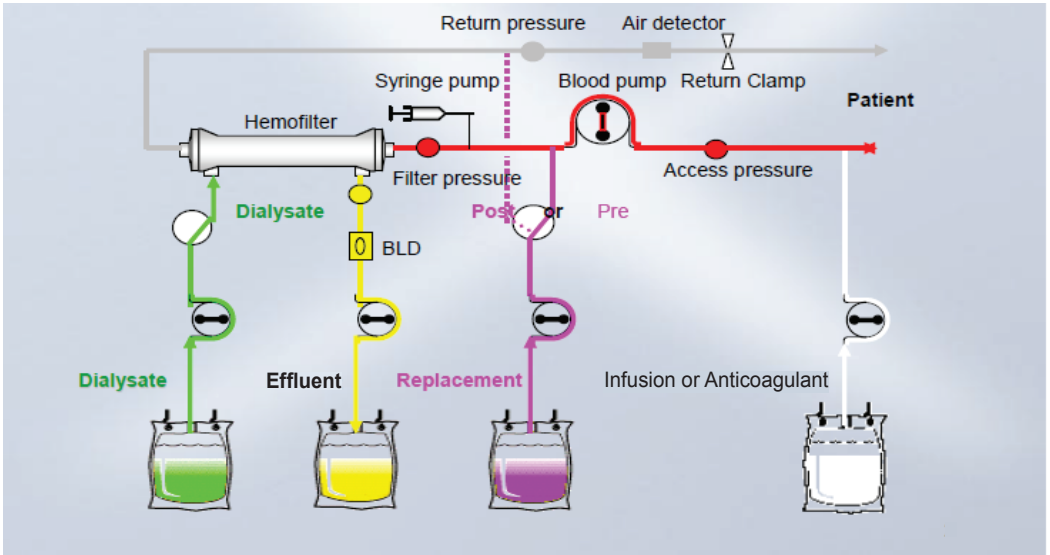

Fig. 4 Continuous Veno-Venous-HaemoDiafiltration (CVVHDF) technique

Replacement fluid

Fluid is removed by convection and has to be replaced to the patient. Management of replacement fluids helps in precise handling of volume in critically ill patients. The fluid can be replaced either pre-or post-filter. Pre-filter replacement prolongs filter life but compromises convection. Post-filter replacement helps in optimal convection but filter life is shortened. Commercially available fluids are deficient in potassium and phosphate. There are also different buffer based fluids like bicarbonate, acetate or lactate, each having its own advantages and disadvantages.

The following recommendations are made regarding replacement fluids:

1. Bicarbonate, rather than lactate or acetate should be used as buffer.
2. The fluids should be judiciously distributed between pre- and post-filter.
3. The filtration fraction should be<25%.
4. Regular measurement of electrolytes should be done – at least 4hourly.
5. Replacement of potassium should be started if serum k^+<4 mmol/L.
6. Replacement can easily be given separately to the patient.

Indications

The continuous therapies are being used in modern ICUs not only for replacement but also as a comprehensive organ support extending their usefulness beyond the kidneys.

1. In patients of AKI, the modality is the treatment of choice in critically ill haemodynamically unstable patients.
2. 2. Its ability of precise volume control leads to precision in fluid removal especially in patients of cerebral and pulmonary oedema. Moreover, in severe metabolic acidosis, hyperkalaemia and refractory fluid overload in the backdrop of haemodynamic instability, CRRT is the modality of choice. In acute liver failure patients it can be used as a bridge therapy before liver transplant.

CRRT has been extremely useful in haemodynamically unstable patients. It has an added advantage of precise volume control which leads to precision in fluid removal, especially in patients of cerebral and pulmonaryo edema. In Patients of sepsis where after the initial adequate fluid resuscitation, a late conservative pattern of fluid removal is advocated, there CRRT comes to the rescue. Moreover, patients who are in severe ARDS, where oxygenation is not an issue, ECCO2R via CRRT might help in reducing the tidal volume further preventing lung injury thus avoiding the complicated process of ECMO.

Conditions where CRRT can be used

1. AKI in septic shock, KDIGO Stage 2/3
2. Cerebral oedema
3. Pulmonary oedema
4. Acute metabolic acidosis in sepsis
5. Hyperkalemia and haemodynamically unstable patients
6. Refractory fluid overload
7. Permissive hypercapnoea.
8. Refractory septic shock
9. Acute liver failure
10. Hyperthermia >40^0C without the expected response to medical therapy
11. Permissive hypercapnoea

Biomarkers of AKI diagnosis

The kidneys is not as lucky as the heart to have biomarkers which promptly diagnose its dysfunction. By the time serum creatinine is raised, more than half of the kidney dysfunction has occurred.

Biomarkers have been used in the diagnosis, progress, and prognosis of AKI with limited success. Some of the prominent biomarkers are serum and urinary NGAL, serum and urinary Cystatin C, KIM-1, L-FABP, IL-18, to name a few.

NGAL (neutrophil gelatinase associated lipocalin) is a 25 kDa protein expressed in neutrophils and different epithelia including kidney tubules. It is released in both urine and plasma and increases within 2 hours of acute kidney injury. It has been found to be a diagnostic as well as prognostic marker in certain studies[6].

Cystatin C is a non-glycosylated LMW cysteine protease synthesized at relatively constant rate and released in the plasma by all nucleated cells. It is freely filtered by the glomerulus and completely reabsorbed by the proximal tubule.Systemic

cysteine C is a measure of GFR. Urinary cystatin C is indicative of tubular dysfunction[7].

Cell cycle arrest markers IGFBP (insulin like growth factor binding protein) and TIMP 2 (tissue inhibitor metalloproteinases 2) have been the latest ones used to diagnose AKI. The product of both(>0.3)(nephrocheck)in urine have been found to be predicting the development of moderate to severe AKI within 12 hours of testing[8-10].

When to start CRRT?

Consensus regarding as to when to start CRRT is yet to be achieved. Most of the earlier studies in the initial part of the decade were in favour of early start of therapy[11,12]. However, the criteria of early therapy were vague. The RIFLE, AKIN and KDIGO classification has helped in classifying AKI according to the increasing order of severity. The recent trials of AKIKI[13] and ELAIN[14] have contradictory results.Whereas ELIAN study is in favour of starting CRRT early at KDIGO II, AKIKI and the other recent studies like STARRT-AKI, IDEAL-ICU and AKKI II trial concluded that there is no advantage of early CRRT over late. The general consensus is to individualize patients and start CRRT accordingly. Figure 4 shows the practical approach in starting RRT.

AKI Staging	Urine output	RIFLE	AKIN	KDIGO
1	< 0.5 ml/kg/hr for 6-12 hours	RISK serum creatinine>1.5 × 7 days. Sustained for > 24 hours	Rise in serum creatinine 1.5-2 × baseline or 0.3 mg/dl absolute increase over 48 hours	Rise in serum creatinine 1.5-1.9 time the baseline over 7 days or 0.3 mg/dl absolute increase in 48 hours
2	<0.5 ml/kg/hr >12 hours	INJURY Serum creatinine >2 times	Serum creatinine 2-3 times the base line	Serum creatinine 2-2.9 times the baseline
3	<0.3 ml/kg/hr > 24 hours or anuria for 24 hours	FAILURE Serum creatinine >3 times the baseline or serum creatinine increase >4mg/dl (with increase in 0.5 mg/dl) or initiation of RRT	Serum creatinine >3 times the baseline or serum creatinine increase >4mg/dl (with increase in 0.5 mg/dl) or initiation of RRT	Serum creatinine greater than 3 times the baseline or serum creatinine increase to 4mg/dl or initiation of RRT
		LOSS: complete loss of kidney function > 4 weeks		
		ESKD: ESKD for refractory fluid overload Refractory septic shock Acute liver >3 Months		

At what flow rate?

Dosage of CRRT is completely different from that of IHD. In IHD, the rate of clearence of urea i.e., KT/V (UREA) is considered to be the dosing option. Critically ill patients, however, are having a variable volume of distribution, are metabolically unstable, on vasopressor and having some residual kidney function left, making them completely different from relatively stable patients. In CRRT, dose is calculated on the basis of the rate of effluent volume.

In the earlier part of this century, many users were in an opinion to use a higher dose (40 ml/kg /hr) of effluent volume which was found to have mortality benefit over lower doses (25ml/kg/hr)[15]. However, this was negated by ATN and

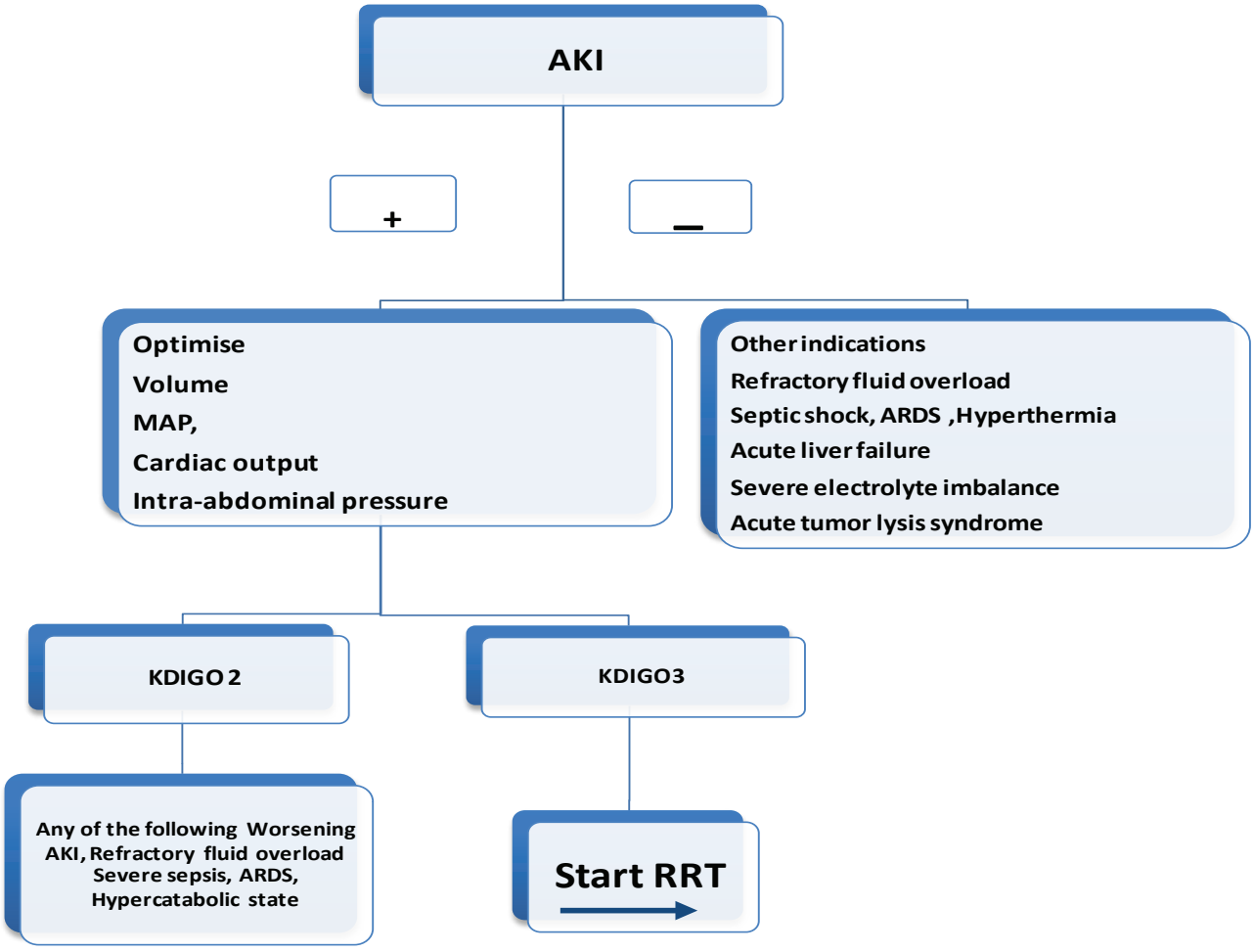

Fig. 5 Practical Approach in starting RRT

RENAL trials[16,17] which showed that high intensity RRT does not have any mortality benefit over their lower counterpart The general consensus is to use a dose of 25ml/kg/hr of effluent volume. However, in order to achieve the desired dose, the dose prescribed should be higher as there might be multiple stoppage times affecting the dosage as shown by the DOREMI study group[18].

The recommendation is

1. Effluent volume of 25ml/kg/hr is the recommended dose.
2. Prescribe a higher dose to achieve this dose.
3. Dosage must be individualized according to patient needs.

Anticoagulation CRRT

Anticoagulation is essential to keep the filter patent. The most frequent anticoagulant used is unfractionated heparin in a dose of 5-10 U/kg/hour. The APTT is monitored every 6 hourly and values should be kept between 45-50 seconds (1.5 times the normal). Heparin may complicate the *in vivo* coagulation process thus causing harm to critically ill patients. Citrate, is used as a regional anticoagulant, does not alter the coagulation parameters of the patient. It is given in the form of sodium citrate. Post filter ionized calcium level should be 0.3mmol/l. Proper replacement of calcium has to be done due to avoid hypocalcemia. Hypernatremia, metabolic alkalosis and hypocalcaemia are side effects. In liver failure, citrate is not metabolized resulting in high anion gap metabolic acidosis (total Ca/ ionised Ca >2.25-2.5 mmol/l). Certain centres use LMWH (low molecular weight heparin) and prostaglandins as anticoagulants.

When to stop?

- AS PER KDIGO 2012 (19), RRT is discontinued when it is no longer required, either because intrinsic kidney function has recovered to the point that it is adequate to meet patient needs, or because RRT is no longer consistent with the goals of care. However, it should be made sure that the patient is in optimal condition (haemodynamics, volume and electrolyte status, metabolic status) before RRT is terminated. Instead of abrupt stoppage of CRRT it is advisable to shift to conventional intermittent modes till the patient completely regains his/her renal functions.
- Protocolised weaning from CRRT is practiced in many centres. If the patient condition is stable haemodynamically, and his respiratory functions are stable, the probable cause and sequel of AKI has been addressed and the urine output is >30 ml/hour, then measure the 24-hour urinary creatinine in the intra-dialytic period. If the value of urinary creatinine is >5.2 mmol/L, cessation of CRRT could be attempted.

Nutrition in CRRT

CRRT causes a phenomenon called Depletion syndrome. There is massive loss of amino acids, water soluble vitamins, micronutrients, and elements like Zinc during the process. The goal is to achieve a total energy intake of 20–30 kcal/kg/d in patients with any stage of AKI[20]. Energy provision should be composed of 3–5 (maximum 7) g per kilogram body weight carbohydrates and 0.8–1.0 g per kilogram body weight fat. A normal-to-high protein replacement is indicated in these situations. Administer 0.8–1.0 g/kg/d of protein in non-catabolic AKI patients without need for dialysis. Protein is administered at an amount of 1.0–1.5 g/kg/day in patients with AKI on RRT and up to a maximum of 1.7 g/kg/d in patients on CRRT and in hypercatabolic patients. In absence of contraindications enteral route is always preferred over parenteral nutrition.

Antibiotics in CRRT

Antibiotic dosing in CRRT is a complex phenomenon. Close monitoring of drugs wherever possible should be done. Loading dose should never be compromised. Maintenance doses should be changed either by increasing the duration especially in concentration dependent antibiotics, or by decreasing the dose but keeping the frequency of doses same in cases of time dependent antibiotic. It is preferable to use single substances over combination therapies. One should be aware of the risk of under-dosing during effective CRRT. Antibiotics getting adsorbed in membrane—like fluoroquinolones, need higher dosing. Higher doses should also be considered if convective therapies are used rather than diffusive therapies. Creatinine clearance is a good modality to calculate dose but it ignores tubular drug handling. Therapeutic drug monitoring, if possible, is the best option to decide on doses of drugs in CRRT[21].

Conclusion

CRRT is gaining greater acceptance and becoming more widely utilised for treatment of both renal and non-renal indications. It is more of a renal support rather than replacement.In the population of critically ill patients CRRT is one of the best RRT options for those hamodynamically unstable patients who also needs precise volume control. An Intensivist plays a very important role through setting up the right prescription, continuous monitoring and identification of any problem and resolving it at the earliest for the success of therapy.

Table 1. Antibiotic dosage chart in CRRT

Sl. No.	Drugs	Route of elimination	Time dependent or Concentration dependent	Drug Dose CVVH	Drug Dose CVVHD/CVVHDF	Drug Dose IHD
1.	Acyclovir	Renal	Time dependent	5-7.5 mg/kg q 24h CNS infections 10mg/kg q 12h	5-7.5 mg/kg q 24h CNS infections 10mg/kg q 12h	1.5 mg/kg q 24h CNS infections 5mg/kg q 24 h
2.	Ampicillin	Renal	Time dependent	3g q 12h	3g q 12 h	1-2 g q 12 h
3.	Aztreonam	Renal	Time dependent	1-2 g q 12h	2 g q 12h	1 g q 24h
4.	Cefepime	Renal	Time dependent	1-2 g q 12h	2 g q 12h	2 g q 24h
5.	Cefriaxone	Renal	Time dependent	1-2 g q 12h	2 g q 12h	1-2 g q 12h
6.	Ceftazidime	Renal	Time dependent	1-2 g q 12h	2 g q 12h	1g q 12h f/b 1g post HD
7.	Ciprofloxacin	Renal	Concentration dependent	200 mg q 12h	200-400 mg q 12h	400 mg q 24h
8.	Colistin	Renal	Concentration dependent	2.5 mg/kg q 48h	2.5 mg/kg q 48h	1.5 mg/kg q 24h
9.	Polymyxin B	Hepatic	Concentration dependent	15000-25000 U/kg/day q 12h	15000-25000U/kg/day q 12h	No data
10.	Fluconazole	Renal	Time dependent	200-400 mg q 24h	400-800 mg q 24h	400 than 400mgq 24h
11.	Imipenem	Renal	Time dependent	250 mg q 6h or 500 mg q 8h	250 mg q 24h	No data
12.	Levofloxacin	Renal	Concentration dependent	250 mg q 24h	250 mg q 24h	500 mg than 500 mg q 24h
14.	Moxifloxacin	Hepatic	Concentration dependent	400mg q 24h	400 mg q 24h	400 mg q 24h
15.	Piperacillin	Renal	Time dependent	2.25 g q 6h	2.25-3.375g q 6h	2.25 q 24 h
16.	Vancomycin	Renal	Time dependent	1 g q 48 h	1g q 24h	15-20 mg/kg q 24h
17.	Voriconazole	Hepatic	Time dependent	4 mg/kg po q 12h	4 mg/kg po q 12h	4 mg/kg po q 24h

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CASE REPORT

Left Tibial Osteomyelitis in a Middle Aged Male due to Burkholderia Pseudomallei

Arshad Akeel[1], Santhosh Sriganth[2], Sivaranjani Sellamuthu[3]

Abstract

Melioidosis caused by Burkholderia pseudomallei, gram negative bacilli, predominantly found in soil and water. Melioidosis can present as pneumonia, pneumonia with septicemia, abscess in various organs and very rarely it involves musculoskeletal system and it presents as osteomyelitis, septic arthritis, or soft tissue abscess. Here we present a case of 32-year-old male, with no known comorbidities who presented with a history of fever, weight loss, loss of appetite and dry cough for 6 months and left knee pain for past 1 year. On evaluation, he was found to have anaemia, splenomegaly. Blood and urine cultures were negative. Magnetic resonance imaging of the left knee showed features of left tibial osteomyelitis with a soft-tissue abscess and myositis. Patient underwent saucerization and debridement. His bone biopsy culture showed growth of Burkholderia pseudomallei. The patient's fever and left knee pain subsided after treatment with IV antibiotics.

Key Words

Osteomyelitis, Saucerization and debridement, Burkholderia pseudomallei

Introduction

Osteomyelitis is an infection of the bone which can be acute or chronic at presentation. It is mostly caused by pyogenic organisms which spread through the blood stream, fractures or surgery. Melioidotic osteomyelitis, which is a rare cause of osteomyelitis, caused by an ubiquitous Gram negative soil pathogen, Burkholderia pseudomallei[1]. This infection is transmitted through cutaneous inoculation, inhalation or ingestion[2]. It is commonly found in the soil and ground water of many tropical and subtropical regions[3]. Patients with diabetes mellitus, chronic renal failure, alcoholism and immunocompromised status are more susceptible to Melioidosis[5]. The clinical spectrum of melioidosis ranges from pneumonia, cutaneous infection to disseminated disease with fatal septicemia[1]. There is no specific clinical presentation of melioidosis of bone and joints, and it mimics different forms of osteomyelitis, septic arthritis and rheumatoid disorders. It mainly causes infections in knee and hip joints. It also affects the shoulder and other joints[6]. Routine diagnosis of melioidosis is done by cultivation of Burkholderia pseudomallei from clinical specimens[4]. Treatment is surgical debridement of the involved bone and IV antibiotics for a longer duration.

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Case Report

A 32-years old male from Assam, residing in a rural area Baksa district, Bhutan border a, daily wages labourer, presented with a 6-months history of fever, weight loss around 13 kilograms, loss of appetite, dry cough, and left knee pain for past 1 year. He gave no history of breathing difficulty, chest pain, abdominal pain, vomiting, loose stools, altered sensorium and headache. He was evaluated elsewhere in the past one week (28-11-2023 to 05-12-2023) where he was found to have anaemia, elevated liver enzymes, elevated lactate dehydrogenase (LDH) and ferritin. Rapid card test done at a private Hospital on 26-11-2023 was positive. Repeated card test on 28-11-23 was negative and smear was positive for P. falciparum and P. rivax. He was treated with IV artesunate and oral primaquine. In view of persistent symptoms, the patient was admitted in our hospital for further evaluation and management.

On examination, the patient was conscious, oriented, and severely emaciated. There was pallor and no signs of clubbing and lymphadenopathy. Per-abdomen examination showed splenomegaly. Local examination of left knee showed non-tender diffuse swelling with warmth. There was no restriction of knee movements. His blood pressure was low on presentation. Basic investigations showed anaemia, elevated transaminases, mildly elevated total bilirubin and elevated erythrocyte sedimentation rate [Table 1]. Chest X ray was normal [Fig. 1]. Ultrasound abdomen showed mild splenomegaly. Blood and urine cultures were sent. Patient was started on IV Meropenem and IV Doxycycline. 2 units of packed red blood cells were given. Patient's haemodynamics improved gradually but he continued to have left knee pain. Blood and urine cultures were negative.

Table 1

PARAMETERS	PATIENT'S VALUE	NORMAL VALUE
Haemoglobin	4.9 gms/dl	13-18 gms/dl
WBC (white blood cell)	4460	4000–11,000
Platelet count	1,50,000	1,50,000–4,10,000
Erythrocyte sedimentation rate	104 mm/hr	0–15 mm/hr
Total bilirubin	1.7 mg/dl	0–1.3 mg/dl
Direct bilirubin	0.9mg/dl	0–0.4mg/dl
SGOT (Aspartate aminotransferase)	70 U/L	<35 U/L
SGPT (Alanine aminotransferase)	110	<45 U/L
ALP (Alkaline phosphatase)	212	<128 U/L

Malarial parasites, LeptospirosisIgM, Scrub IgM- NEGATIVE

HbsAg, Anti-HCV, HIV- Negative

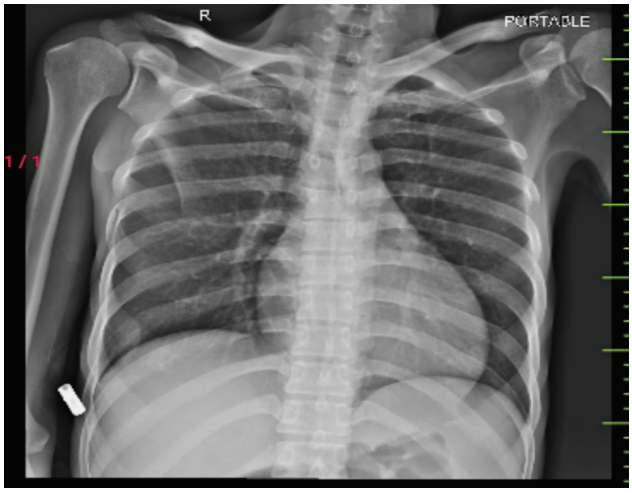

Fig. 1

Magnetic resonance imaging showed [Fig. 2] An intramedullary collection extending for a length of approximately 4.7 cm with maximum thickness of 6 mm, with central T1 hypointensity and peripheral hyperintense rim, is noted at anterolateral cortex of the tibia. Surrounding oedema is noted. In its inferior aspect, subperiosteal extension of this collection is noted with mild elevation of the corresponding periosteum. In its superior aspect, cortical breach (cloaca) of the adjoining anterolateral cortex is seen with extension of the collection to the surrounding soft tissue. Areas of restricted diffusion are seen within this collection. Heterogeneous peripheral post-contrast enhancement is noted.

Features suggestive of acute osteomyelitis with associated soft tissue abscess and myositis.

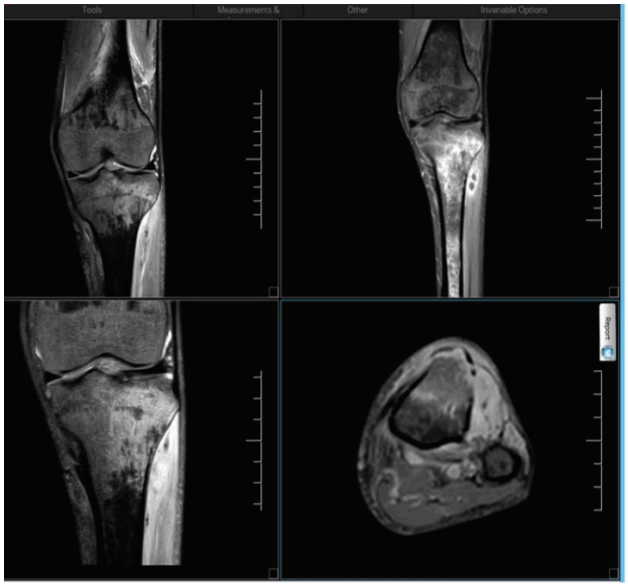

Fig. 2

Saucerization and debridement of left tibia was done.

Biopsy showed features of necrotising granulomatous osteomyelitis [Fig. 3a & 3b].

Bone biopsy Gram's stain showed moderate pus cells and no bacteria. Fungal stain was negative. Xpert-MTB was negative. Bone biopsy showed growth of Burkholderia pseudomallei. Patient was discharged on IV Ceftazidime 2Gm 1-1-1 for 4 weeks and oral T. Bactrim-Ds 1 B05 for 6 weeks.

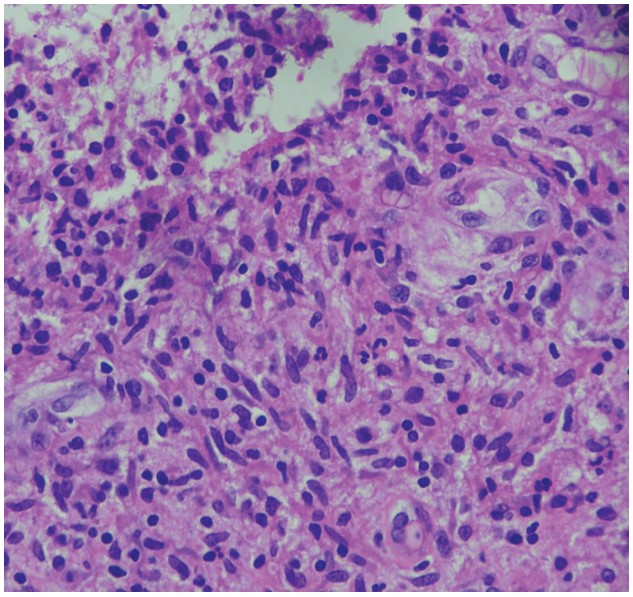

Fig. 3a

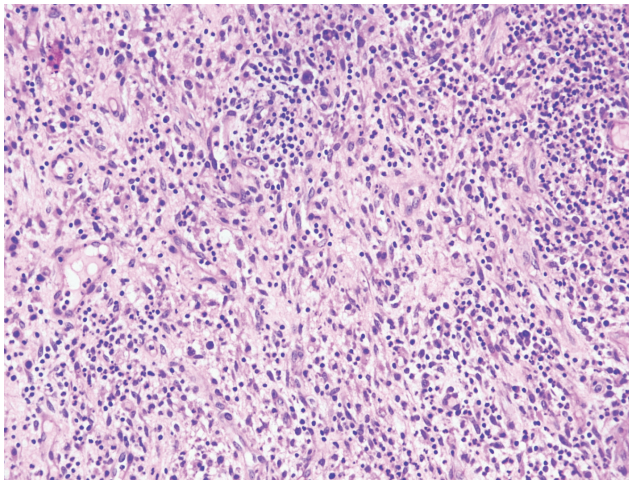

Fig. 3b

Discussion

Burkholderia pseudomallei, sometimes known as B. pseudomallei, is the causal agent of melioidosis, a serious and sometimes fatal infectious disease[6]. Burkholderia pseudomallei is an aerobic, motile, intracellular, non-spore-forming soil saprophyte that lives in moist soil and surface water[6]. It is a bipolarly stained, oxidase-positive, Gram-negative bacillus that appears as a safety pin in the Gram stain film[6]. B. pseudomallei is resistant to several antibiotic classes, including rifamycins, aminoglycosides, penicillins, and first- and second-generation cephalosporins[6].

Whitmore and Krishnaswami initially identified melioidosis in septicemia patients receiving intravenous morphine in Burma (now Myanmar) in 1912[6]. The bulk of cases are reported from tropical latitudes between 20 N and 20 S, which correspond to Southeast Asia and Northern Australia[6]. Sporadic instances have also been reported from India, Sri Lanka, Malaysia, Pakistan, Indonesia, Japan, and Bangladesh[6].

The bacteria B. pseudomallei is found in the ground with depths of around 8-10 cm from surface, these bacteria usually move to the upper layer of the soil during rains and then multiplies[3]. Naturally acquired infections are due to exposure via broken skin, ingestion, or inhalation[3]. Occupations like farmers and gardeners in tropical/subtropical regions encounter more exposure to soil[3]. Similar to this, our patient had exposure to soil as a risk factor.

Melioidosis commonly impacts sufferers with underlying ailments along with diabetes mellitus, heavy alcohol consumption, lung disorders, corticosteroid use, malignancy, thalassemia, preceding trauma, coronary heart disorder and/or cardiac failure, and surgery. Other threat elements consist of splenectomy, aplastic anaemia, cystic fibrosis, glucose-6 -phosphate dehydrogenase deficiency, and systemic lupus erythematosus[6].

Acquisition in bone and joint infections is usually via direct spread through small skin abrasions, wound infections and abscess or hematogenous spread in patients who presented with another primary diagnosis, such as pneumonia or septicemia[6]. There is no specific clinical presentation, and it mimics different forms of osteomyelitis, septic arthritis Infections, and rheumatoid disorders[6]. The clinical features in septic arthritis are swelling, tenderness, redness, and heat around the joints[6]. Either single or multiple bone or joint involvement is observed[6]. B. pseudomallei mainly causes infections in knee and hip joints[6]. It also affects the shoulder and other joints[6].

Lack of awareness about the disease, limited laboratory resources to isolate the organism, and confusion with other infectious diseases such as Mycobacterium tuberculosis, may lead to the misdiagnosis of melioidosis[6]. Isolation of B. pseudomallei from the specimen is the gold standard investigation[6]. A modified Ashdown media which contains colistin is currently used for isolation of the organism[6].

The recommended treatment for musculoskeletal melioidosis is divided into an initial intensive phase of 6 weeks followed by the eradication phase of 6 months[7]. During the intensive phase, intravenous (IV) ceftazidime 2 gm every eight hourly or meropenem 1gm every eight hourly can be given depending on the patient's clinical condition and severity[7]. The eradication phase mainly consists of oral trimethoprim/ sulfamethoxazole therapy[7]. Oral second drug is also considered if the disease is severe[7]. A similar recovery was seen in our patient after receiving intense therapy with IV CEFTAZIDIME 2 Gm TDS.

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CASE REPORT

Pulmonary Embolism and Bleeding Ulcerative Colitis – Anti-coagulate or Not ?

Sayak Roy[1], Tamer Elderini[2], Pradeep Singh[3]

Abstract

A 50-year-old gentleman came to the accident and emergency (A&E) department with a possible flare-up of his underlying ulcerative colitis (UC). He got admitted as the initial assessment deemed him to be suffering from moderate UC flare-ups. While in-patient, he was investigated for a significant weight loss of 12 kg in 2 weeks and was found to have an incidental pulmonary embolism (PE) in the right lower lobe pulmonary artery branch.

This case report discusses a common situation in an acute medical setting, where we have to take the call of therapeutic anticoagulation even in the face of on-going active bleeding per rectum.

Keywords

Venous thromboembolism, inflammatory bowel disease, ulcerative colitis.

Introduction

Vascular complications as extra-intestinal manifestation of ulcerative colitis (UC) are rare[1].

Pulmonary embolism (PE) is a common cause of preventable death in any part of the world. Out of many risk factors, active ulcerative colitis (UC) increases PE risk by eight times[2].

Patient Information

A 50-year-old gentleman attended the A&E with H/O abdominal pain, increased bowel movements ten times a day, and occasionally mixed with blood and mucous. He was known to the gastroenterology department from his previous UC follow-ups. He reported to have lost 12 kg over the last three weeks.

He received a total of three doses of biological for UC, which he believed did not help at all.

He continued to have flare-ups of his UC and generalized weakness as a result. He never smoked and consumed less than 14 units of alcohol weekly. He has been on prednisolone since his last admission. at the time of admission, he was on 30 mg./day which needed to be weaned by 5 mg every ten days.

Clinical Findings

On examination, he had signs of mild dehydration and generalized abdominal tenderness without any signs of acute gut perforation. He was investigated initially with routine chest X-ray and abdominal X-ray that ruled out any chest infection, gut perforation signs, or any signs of toxic megacolon.

Diagnostic work-up and in-patient course

He was investigated with Computed tomography

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(CT) of the chest, abdomen, and pelvis (CT-CAP) given his severe rapid weight loss over a few weeks to rule out any underlying malignancy. The CT showed a 12 mm lung nodule in the periphery of the left lower lobe, PE in the right lower lobe pulmonary artery branch, diffuse mural thickening of the sigmoid colon, descending colon, caecum, and ascending colon, and a few segments of the dilated small bowel and probably associated strictures, suggestive of acute colitis. His biopsy report (samples taken from the descending colon, sigmoid colon, and rectum) from January 2024 also showed a moderate increase in inflammatory infiltrate in the lamina propria along with moderate active inflammation in the form of cryptitis and crypt abscess formation; no granulomas were seen and, there were no features of dysplasia or malignancy.

Table 1. Blood trends on admission and after treatment

Blood count				
Component Ref Range & Units	3/3/24	2/3/24	1/3/24	7/2/24
White Cell Count 3.7 - 9.5 10*9/L	14.5	16.5	27.0	8.8
Red Cell Count 4.30 - 5.70 10*12/L	4.46	4.50	5.03	3.80
Haemoglobin 133 - 167 g/L	112	116	132	100
Haematocrit 0.390 - 0.510 L/L	0.370	0.367	0.411	0.326
MCV 82 - 98 fL	83	82	82	86
Platelet Count 140 - 400 10*9/L	392	374	431	223
Neutrophils 1.70 - 6.10 10*9/L	12.69	14.25	23.25	6.09
Renal profile				
Sodium 135 - 145 mmol/L	132	126	126	138
Potassium 3.5 - 5.3 mmol/L	5.1	4.9	6.0	3.2
Creatinine 61 - 123 μmol/L	105	115	124	63
eGFR by CKD-EPI mL/min/1.73m2	70	63	57	>90

Blood results showed very high inflammatory markers, raised procalcitonin (1.4) units and an acute kidney injury (AKI) alert on day 1 of admission (Table 1), which reverted to normal after proper hydration and intravenous antibiotic use. The increased procalcitonin raised the probability of an underlying infective aetiology on top of the UC flare-up and was treated initially with empirical triple antibiotic cover for intra-abdominal sepsis with amoxicillin, amikacin, and metronidazole as per the trust guidelines. Stool samples, sent for clostridium infection and routine culture, came back negative for any *c. difficle* toxin or any infective aetiology, and antibiotics were de-escalated with the continuation of hydrocortisone 100 mg four times daily, IV fluids, mesalazine four times a day, paracetamol as per need. Gastroenterology advice was sought. His initial hyperkalemia due to the AKI was treated as per trust protocol with IV insulin, calcium gluconate, and fluids. Blood on the following day showed marked improvement in inflammatory markers and resolution of the AKI (Table 1).

Due to active bleeding, giving a therapeutic dose of low molecular weight heparin (LMWH), enoxaparin, was risky as it was going against the absolute risk for anti-coagulation in any active bleeds. Hence, the decision was made to discuss with haematology colleagues, who advised starting enoxaparin standard single dose and, if the bleeding worsened, changing to a split dose. He was also advised to switch to direct oral anticoagulants (DOAC) when the diarrhoea improvoed with no bleeding. He was put on a total therapeutic dose of LMWH and was monitored closely. Regular blood tests were done to check for any drop in haemoglobin. His bleeding improved gradually over a few days, and he was finally discharged on DOAC, rivaroxaban, till the anti-coagulation clinic reviewed him.

Discussion

UC is a part of inflammatory bowel disease (IBD). Active UC, in particular, leads to an increase in factor VIII activity, elevates fibrinogen levels, and accelerates thrombin generation, all due to the systemic inflammation related to the disease[3]. The other factors leading to the thrombotic state are the production of cytokines (TNFα, IL-1–3, and IL5), increased platelet activation, and increased levels

of thromboxane B2 and beta-thromboglobulin levels[4,5]. Both arterial and venous thromboembolisms can happen in the context of IBD[6] – arterial being a cerebrovascular disease, ischaemic heart disease, mesenteric ischaemia and, peripheral artery disease; venous being cerebral vein thrombosis, catheter-related thrombosis, PE, Budd-Chiari syndrome, porto-mesentric vein thrombosis and, deep vein thrombosis (DVT). An international consensus in 2020, involving 14 international IBD experts and three thrombosis experts from 12 countries, has come up with recommendations of – LMWH or fondaparinux over heparin as VTE prophylaxis and even goes on to recommend VTE prophylaxis is indicated in ambulatory patients with active IBD flare till they get into remission[6]. VTE prophylaxis has not been seen to increase further bleeding from the gastrointestinal tract in active IBD patients. Patients with VTE predisposing factors like factor V Leiden or prothrombin gene mutation, if initiated on infliximab, must be aware that there have been reports of VTE with infliximab initiation[7,8]. Patients can also develop VTE after starting steroids for the control of active IBD flare[9]. The exact reason for PE in our patient was not very clear, and it was thought to be due to the combined effects of dehydration, active UC, previous infliximab injection, and ongoing steroid use.

Conclusion

The pathophysiology of VTE in active IBD is yet to be understood. Although we have newer drugs to tackle refractory UC, these new drugs do have the potential to cause VTE, which should be kept in mind. Newer recommendations from consensus will help us guide the use of proper anti-coagulants and the duration it needs to be prescribed. Prescribing for VTE in actively bleeding IBD poses a challenge in the setting of acute medicine. A multidisciplinary team approach involving haematology and gastroenterology should be made, and risk-benefit must be discussed. In general, VTE is mandatory for active IBD flare-ups despite active bleeding, as this state itself is pro-thrombotic. If there is a massive bleed or severe rapid drop in haemoglobin, we can use mechanical VTE prophylaxis, like intermittent compression stockings, as a temporary measurement, switching to LMWH as early as possible.

Informed Consent

Written informed consent to publish in this medical journal has been taken from the patient.

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CASE REPORT

Unpacking Pandora's Box: Hypoparathyroidism With Extrapyramidal Symptoms

Nishat Anjum[1], Kaushik Ghosh[2]

Abstract

Identifying a reversible cause in neurological disorders is crucial when treating patients. We encountered a middle-aged female patient in the emergency department presenting with active generalized tonic-clonic convulsions. Upon assessment, she was found to have primary idiopathic hypoparathyroidism, characterized by symmetrical intracranial calcifications that extended beyond the extrapyramidal system, impacting the cortex and cerebellum. This case highlights an atypical presentation of a common condition, demonstrating the reversible neurological implications linked to idiopathic hypoparathyroidism.

Keywords

Extrapyramidal symptoms, hypopara-thyroidism, convulsions, intracranial calcification, Fahr's Syndrome.

Introduction

Hypoparathyroidism is a rare endocrine disorder characterized by low or insufficient level of parathyroid hormone, leading to hypocalcemia, hyperphosphatemia, and hypercalciuria.

Acute features of hypoparathyroidism include tetany, muscle cramps, weakness and paraesthesias. However, a chronic case may be accompanied with convulsions, depression, psychosis, and rarely, with extra-pyramidal symptoms. Common aetiological factors contributing to intracranial calcification include age-related physiological patterns, congenital disorders such as tuberous sclerosis, neurofibromatosis type 2, infiltrative disorders like sarcoidosis, Wilson's Disease, vascular calcifications due to aneurysm and capillary telangiectasia, idiopathic, and metabolic abnormalities.[1] Basal ganglia calcification is not uncommon in a case of hypoparathyroidism; however, extensive bilaterally symmetrical intracerebral calcification extending beyond the extra-pyramidal system is rare, and this case presents with a unique factor of reversible neurological manifestations. Idiopathic hypoparathyroidism, often referred to as a complex puzzle in the field of neurology, remains largely unexplored. The occurrence of simultaneous convulsions and intermittent hemiballismus is exceptionally rare. The accurate diagnosis and effective treatment of such cases contributes valuable insights to the current body of literature.

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Case Report

A 54-year-old female patient was admitted to the emergency room displaying symptoms of tetany and experiencing a sudden and widespread tonic-clonic seizure, alongside a gradual deterioration in muscle strength across all limbs over a period of two years. During the assessment, she exhibited sustained choreo-athetoid movements, dystonia, dysarthria, and decorticate posture without any signs of calcium deposition in the skin or elsewhere. The neurological examination revealed positive Chvostek's and Trousseau's Signs. Evaluation of her motor system indicated increased muscle tone and rigidity, along with atrophy of the small hand muscles [Fig. 1]. The absence of the Babinski reflex and hyporeflexia in deep tendon reflexes as also noted. Comprehensive cranial nerve assessment was normal, with normal function of senses including touch, pain, pressure, temperature, and vibration. The patient's past medical history and family history was revealed to be insignificant.

Her baseline biochemical evaluation showed sodium 141 mmol/l, potassium 3.8 mmol/l, bicarbonate 22 mmol/l, magnesium 1.2 mg/dl (normal 1.7-2.2 mg/dl), phosphorus 6.2 mg/dl (normal 2.5-5.0 mg/dl), corrected calcium 3.06 mg/dl (normal 8.8-10.6 mg/dl), albumin 4.2 g/dl,

Fig. 1 Flexed posture of arms and hands (decorticate rigidity) with wasting of muscles.

urea 35 mg/dl, and creatinine 0.9 mg/dl. Intact parathyroid hormone was 1.76 pg/ml (normal 15-65 pg/ml), and vitamin D3 was 10.8 pg/ml (normal 19.6-54.3 pg/ml). Computed tomography of the brain showed symmetrical extensive calcifications at both cerebellar hemispheres, bilateral basal ganglia, as well as the thalamic and periventricular regions [Fig. 2]. Fundoscopy was normal. Ultrasonography of whole abdomen revealed normal liver and kidney morphology with preserved cortico-medullary differentiation ECG displayed mild Q-T prolongation (QTc 466 ms).

With the help of these investigations, other a etiological factors leading to hypoparathyroidism were ruled out and a diagnosis of primary idiopathic hypoparathyroidism was established. The patient

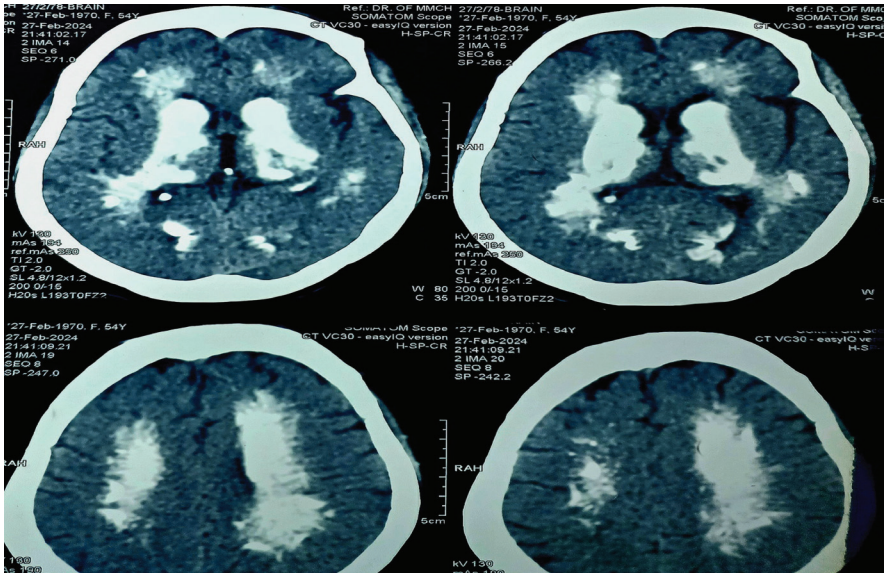

Fig. 2 Computed tomography of the brain showing symmetrical extensive calcifications in both cerebellar hemispheres, bilateral basal ganglia, as well as the thalamic and periventricular regions.

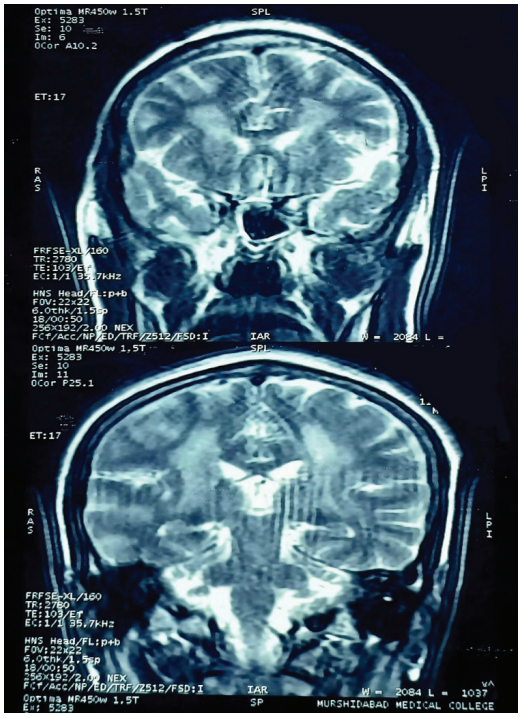

Fig. 3 MRI of the brain showing extensive bilateral calcifications in both cerebellar hemispheres, bilateral basal ganglia, bilateral thalamic and periventricular regions.

was promptly treated with intravenous calcium and magnesium preparations, along with vitamin D3. For convulsions, she was treated with intravenous haloperidol and benzodiazepines. Towards the end of her hospital stay, her electrolyte levels were back to normal, reasonable improvement of neuromuscular symptoms was observed, however, the extrapyramidal features persisted.

Discussion

Idiopathic hypoparathyroidism can be quite challenging to diagnose and may escape detection for years. As demonstrated by this case, it can present with a myriad of neurological/neuro-psychiatric symptoms that may suggest multiple other disorders like dementia, psychosis, epilepsy, cerebrovascular accident, or brain tumor. It is quite uncommon to identify a reversible factor amongst neurological disorders. Seizures can be considered as an acute symptom of hypocalcemia; however it is a risk in general. Thus, it is crucial to exercise caution when a patient presents with convulsions and tetany. Early diagnosis of hypoparathyroidism can lead to the effective management of such symptoms.

In the study of Mitchell et al. 52% of those studied had evidence for basal ganglia calcifications, which is quite commonly seen in a chronic case of hypoparathyroidism[3]. The MRI of brain showed features suggestive of Fahr's Syndrome. Fahr's Syndrome is rare inherited or sporadic neurodegenerative disorder that is characterized by symmetrical bilateral intracranial calcifications involving the areas that primarily control motor functions including the basal ganglia, thalamus, dentate nucleus, cerebral cortex, cerebellum, subcortical white matter, and hippocampus[4]. Neuro-psychiatric examination combined with radiological imaging remains the basic modality for diagnosis of Fahr's Syndrome[5].

Thus, we report a rare presentation in a common disease that focuses on the reversibility of neurological manifestations and underscores the importance of increasing physician awareness of best practices in the management of hypoparathyroidism.

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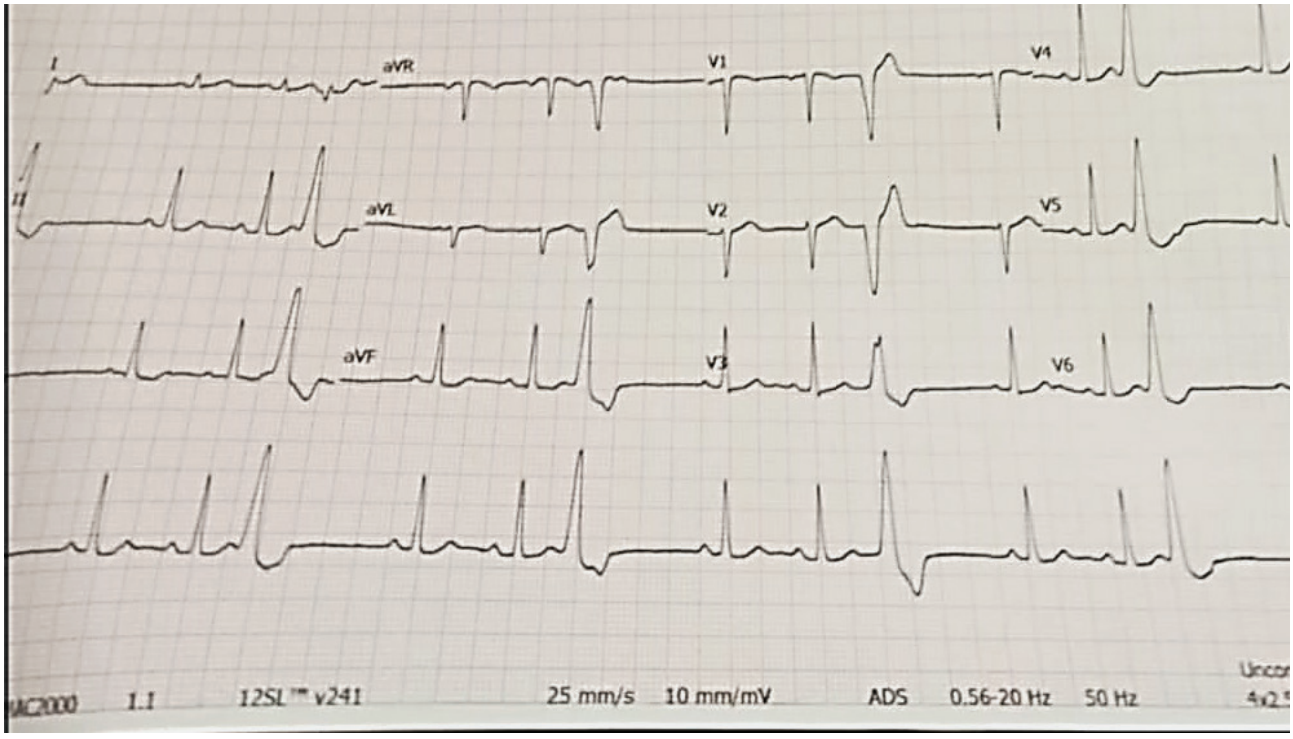
QUIZ

Mainak Mukhopadhyay

30yr old lady presented to OPD with mild dizziness. On examination, she was having an irregular pulse. ECG was suggested.



QUESTIONS

Describe the ECG finding.

Which is the ECG diagnosis?

Justify your answer.

What is the initial management?

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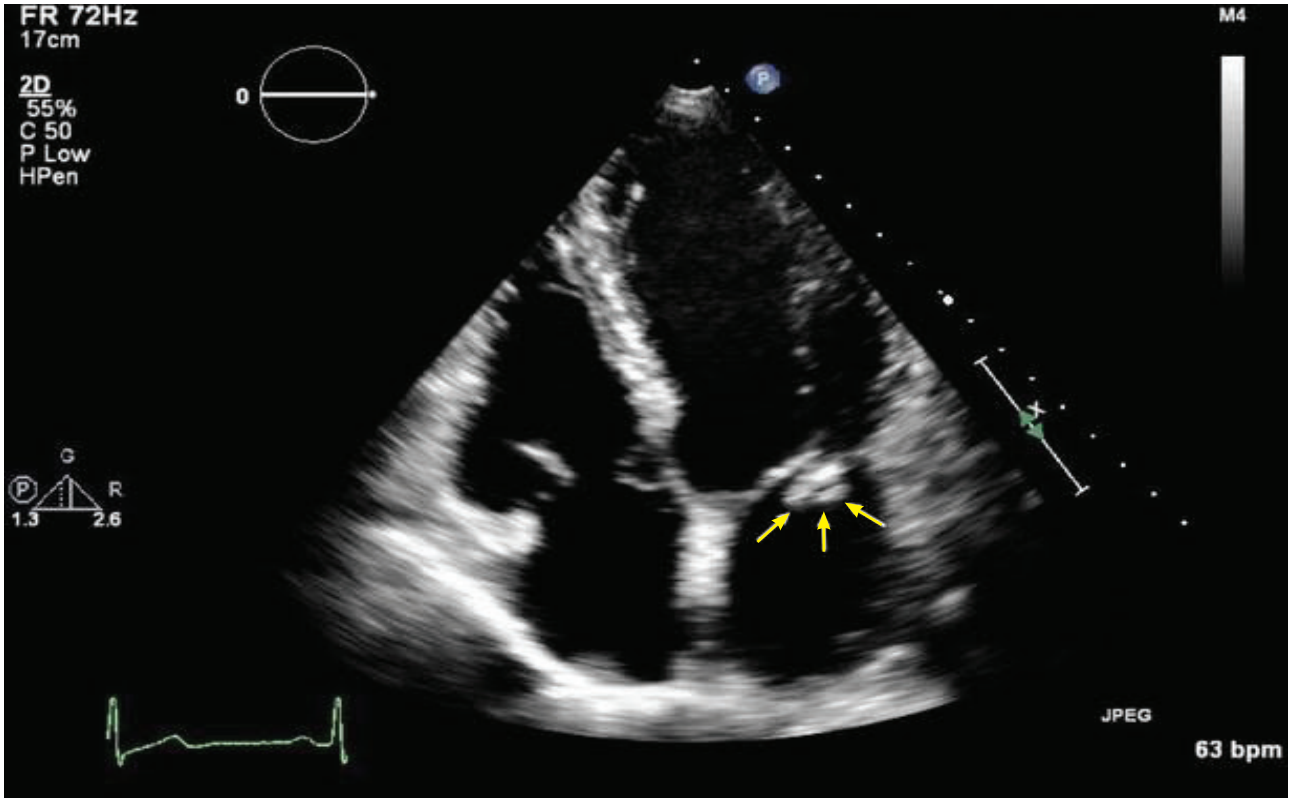
35yr old lady presented to ER with prolonged undiagnosed fever and dyspnea. CVS examination revealed a pan systolic murmur in the apical area. Echocardiography was suggested.



QUESTIONS

1. What is the possible diagnosis of this lady?
2. Which diagnostic criteria is followed to establish the diagnosis?
3. What are the types of PUO?
4. What are the common possible complications of this disease?

CASE REPORT

Cancer Conundrum: Where, Wherefrom, Where Else?

Rajiv Dhall[1], Sabyasachi Ray[2], Venkat Raman Ramanan[3], Amit Mandal[4], Rajib Bhattacharjee[5], Sugat Sanyal[6], Suma Chakrabarthi[7], Sayan Das[8]

Abstract

A 55-year-old lady presented with a long history of dyspeptic symptoms, worse for 1 month with some features of probable liver ailments.

Although, the initial impression was of primarily problems related to the GI hepatic system, hepatic, a multidisciplinary approach and intense and appropriate investigations revealed a diagnosis of malignancy at multiple sites (stomach, breast, and probably ovary) enabling proper planning and treatment.

Key words:

Double primary malignancy, Stomach cancer, Breast cancer, Ovarian mass.

Introduction

This case report is being presented to underscore the importance of looking beyond the obvious, by taking a holistic view of the situation and avoiding tunnel vision. Taking a broader view enabled us to reach the diagnosis of a double primary malignancy (stomach and breast). This working diagnosis enabled the commencement of a well-reasoned treatment regime.

Case Report

History

A 55-year-housewife was admitted in the Gastroenterology Unit of the Hospital in the 2nd week of Feb, 2024 presenting with a long history of dyspeptic symptoms, worse for 1 month, i.e., abdominal pain with nausea, vomiting, sour taste, regurgitation (mainly after dinner), bloating, low appetite, weakness, and weight loss. Her abdominal examination showed diffuse tenderness mainly at epigastrium and flanks. She also had diabetes mellitus and hypertension on treatment. There was no family history of cancer. She had her menopause about 4 years ago and this was uneventful. No addiction or known allergy was there.

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Clinical findings

Abdominal examination revealed moderate ascites; there was no peripheral oedema.Systemic examination was essentially normal except for moderate pallor. There was no jaundice and no other clinical evidence of hepatic dysfunction. Clinically, a mass was noted in the right breast. No hepatosplenomegaly was noted but palpation could not be done properly because of ascites. Gynaecological examination revealed a normal cervix and the rectal mucosa was noted to be free.

Investigations

Blood examination revealed the Hb level to be 10.4 gm/dl and the MCV to be normal at 83.2 fl. The total WBC count was 10,070/cumm. with 82% neutrophils. The peripheral blood smear showed normocytic, normochromic RBCs. The liver function test showed a normal Total bilirubin of 0.4 mg/dl with the total protein value to be slightly low at 5.54 gm/dl (albumin: 2.97 gm/dl, globulin: 2.57 gm/dl). The ALT, AST and Gamma GT levels were normal at 21 U/l, 26 U/l and 18 U/l respectively. The serum creatinine was 0.98 mg/dl.

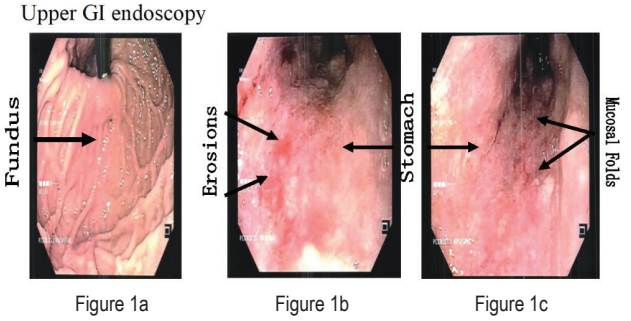

Fig. 1a, Fig. 1b, Fig. 1c Upper GI endoscopy pictures

Grossly abnormal mucosal folds at the mid-third of the stomach with multiple erosions. Gastric mucosar biopsy was taken. Rapid urease test was negative

The blood CA 125 level was moderately raised at 89 U/ml.

Recent Ultrasound examination before admission showed a right adnexal space occupying lesion, gall bladder wall cholesterolosis with thickened wall.

CT scan of the abdomen showed a mass (approx 11 cm x 10 cm) involving the right ovary with grossly heterogeneous enhancement. Gross ascites, diffusely thickened contrast-enhancing stomach wall, extensive para-aortic and peri-portal lymphadenopathy and metastatic peritoneal deposits were also observed (Fig. 2a and 2b).

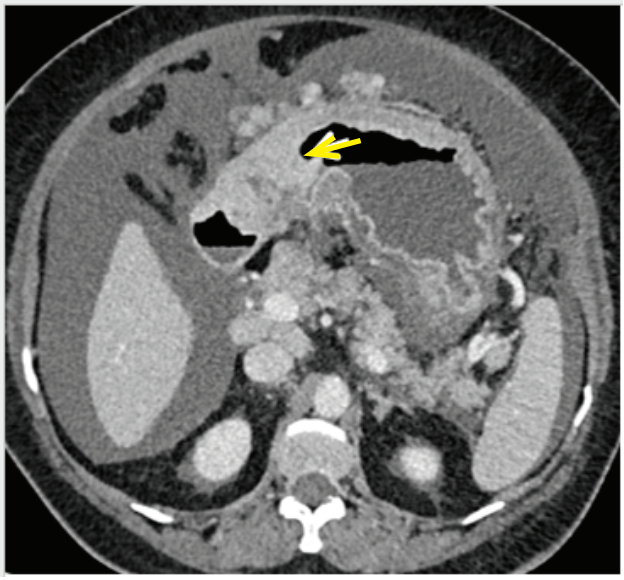

Fig. 2a CT Scan image (Abdomen), Diffusely thickened contrast enhancing stomach wall

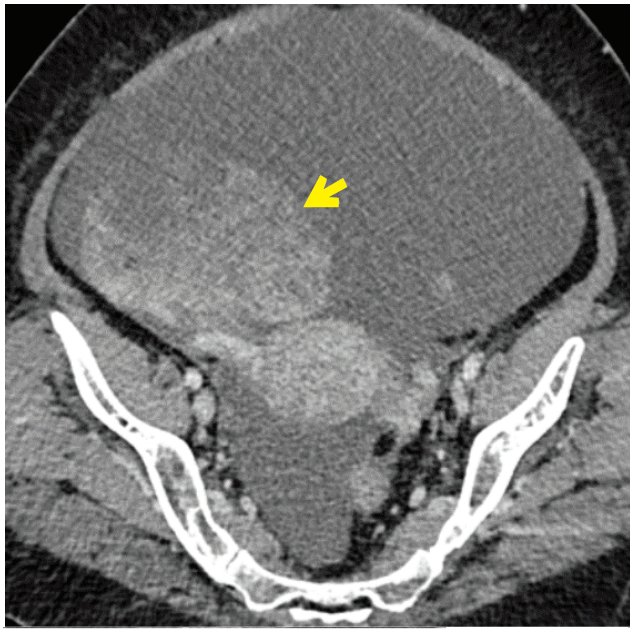

Fig. 2b CT Scan image (Abdomen), A large rounded soft tissue mass is seen involving the right ovary Grossly heterogeneous enhancement with non-enhancing necrotic/ cystic areas seen at the periphery of the lesion

CT scan of the thorax showed no significant abnormality except bilateral mild pleural effusion and adjacent basal atelectasis.

Breast imaging (Mammography and Ultrasonography, Fig. 3a, 3b and 4) revealed a suspicious mass (BIRADS-4) in the right breast and core biopsy was advised.

MAMMOGRAPHY IMAGES (Breast)

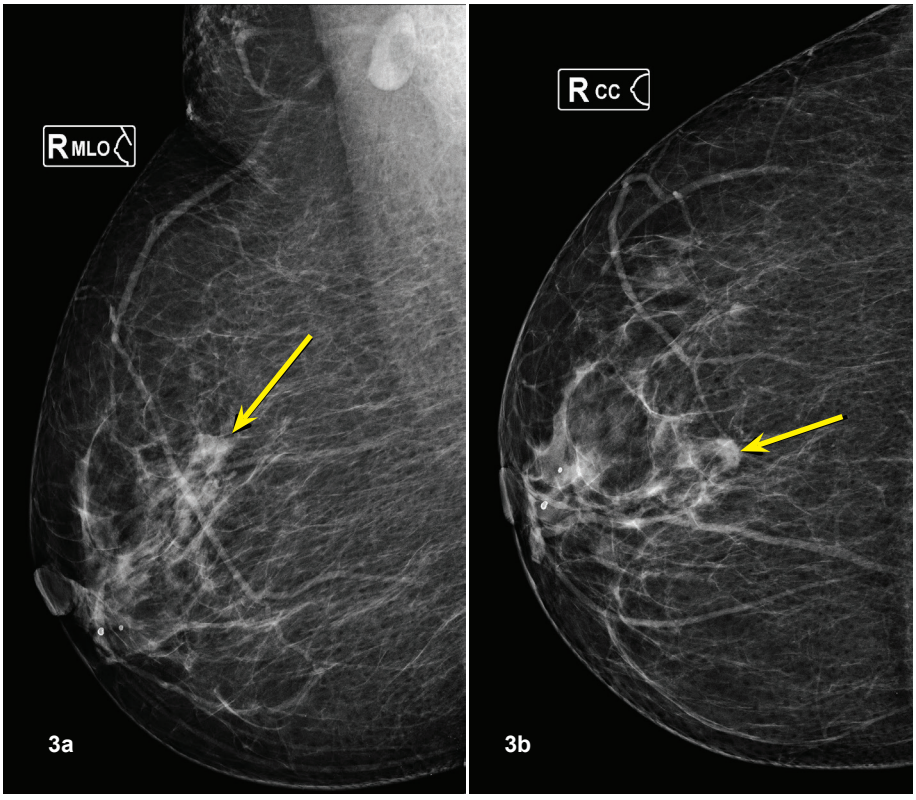

Fig. 3a, 3b Arrows indicates the irregular shaped equal density mass with indistinct margin in the right upper central breast, suspicious for a small malignant neoplasm.

BREAST ULTRASOUND:

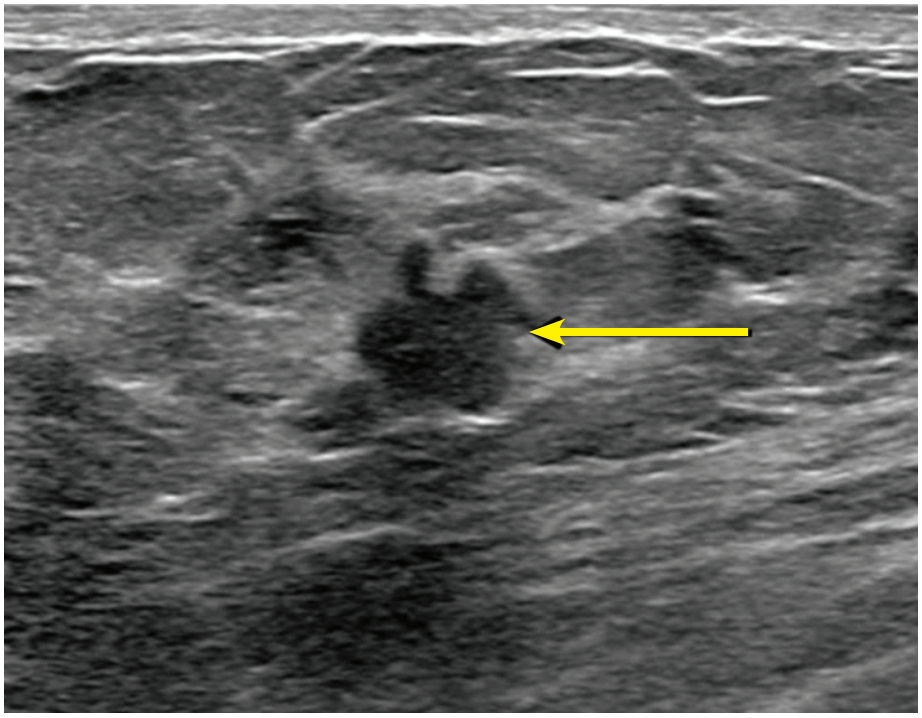

Fig. 4 Arrow shows a 1.2 x 0.8 x 1cm nonparallel irregular shaped hypoechoic mass with indistinct margin in the right upper breast at 12 O'clock position.

The gastric mucosar biopsy showed poorly cohesive carcinoma of signet-ring cell type (Fig. 5). On Immunohistochemistry (IHC) it was found to be HER-2-NEU negative.

HISTOLOGY IMAGES

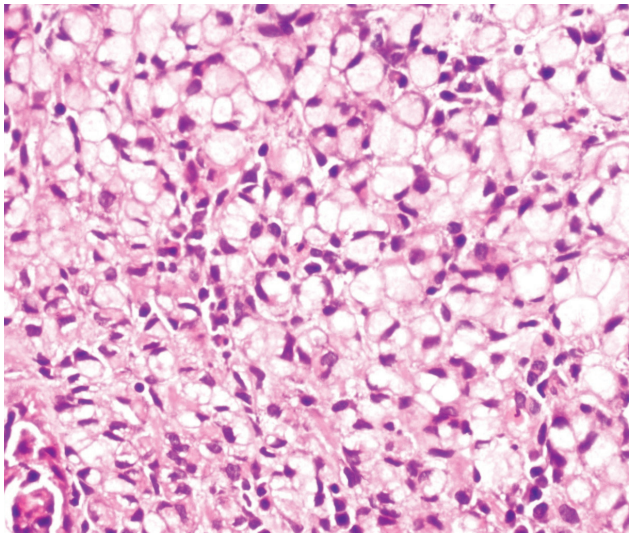

Fig. 5a Poorly cohesive signet ring cell adenocarcinoma of stomach.

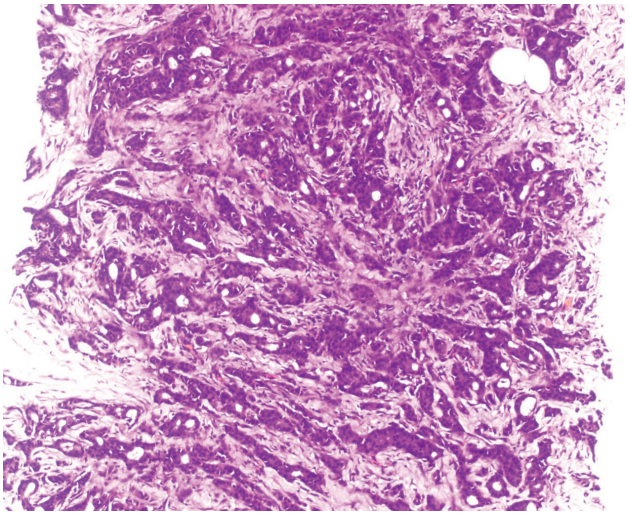

Fig. 5b Invasive Breast carcinoma, NOS (Not Otherwise Specified).

The biopsy on the right breast mass showed infiltrating breast carcinoma, Grade III. The modified Bloom Richardson score was 8 (3+3+2). On IHC, the tumour cells were noted to be ER positive, PR positive with a c-erbB2 Equivocal score of 2+and a Ki-67 proliferative index of 25% - 30%.

The report of a cell block from ascitic fluid showed metastatic adenocarcinoma with signet cell morphology. On IHC, CK7 positivity (50% – 70%), CK20 positivity (30%-50%) and CDX-2 positivity (about 60%) were noted. p53 nuclear positivity (mutant phenotype) was also noted. Morphology and IHC indicated metastatic primary from gastric origin.

Course in the Hospital

Inputs were obtained from Histopathological and Radiological Consultants. Opinion of Medical Oncologist was sought and the case was discussed in the Hospital (Multi-Disciplinary) Tumour Board. It was decided to start the patient on chemotherapy and she was given one dose of IV Oxaliplatin plus started on oral Capecitabine. She was subsequently discharged with advice to take oral Capecitabine and to return for further Chemotherapy.

Discussion

Prima facie this appeared to be a case of Gastrointestinal pathology. However, further probing, the arrival of pending reports and the adoption of a multidisciplinary approach soon made it clear that we were dealing with a double primary (stomach and breast) source of malignancy. Had the rather inconspicuous gastric lesion and the suspicious breast lesion not been picked up and biopsied, we would not have proceeded further on to this diagnosis. Although right-sided breast carcinoma can cause ascites and Krukenberg tumour of the ovary, ovarian and breast tumour co-existence is also well known. However in this case, morphology and IHC suggested the malignant ascites to be metastatic to the gastric primary. Therefore, the gastric and breast malignancies in this case seem to be independent entities.

Multiple primary malignancies are now being increasingly encountered. In a retrospective study (Jena *et al,* 2016)[1], 13 cases of multiple malignancies were detected over a 5-year study period (2 being metachronous, i.e. detected more than 6 months apart and the rest synchronous). The incidence was higher in females with the breast being the most commonly involved organ. Nguyen *et al* (2023)[2] reported a very rare case of 4 primary cancers in 4 different sites in a 63-year-old lady. They concluded that regular follow-up of cancer patients is necessary not only to detect progression or recurrence but also the occurrence

of another primary. Testori *et al* (2015)[3] reported the case of a 66-year-old male with 4 synchronous primary malignant tumours. They concluded that multiple malignant tumours pose a real challenge to the clinician and every effort should be made to avoid a misdiagnosis. Overall, the frequency of multiple primaries is reported in the range of 2–17% (Vogt *et al*, 2017)[4].

In our case, double primary cancer has already been detected. Of course, the right ovarian mass also needs to be evaluated (the left ovary was reported to be normal on CT scan) but upfront chemotherapy was deemed to be appropriate in the first instance considering the entire clinical setting. Further follow-up is essential to track the course of the disease and to offer suitable interventions as and when necessary.

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CASE REPORT

Aviptadil In The Management Of Acute Respiratory Distress Syndrome (ARDS) Induced By Glyphosate Herbicide

Subhadip Pal

Abstract

Acute Respiratory Distress Syndrome (ARDS) presents a significant global health burden, affecting millions annually with diverse underlying causes. Glyphosate poisoning, while not conventionally linked to ARDS, can induce severe pulmonary inflammation potentially progressing to ARDS. Aviptadil, a synthetic vasoactive intestinal peptide (VIP), emerges as a promising therapy for ARDS, offering anti-inflammatory, antioxidant, and bronchodilatory effects. Here, we present the case of a 38-year-old male with ARDS following Glyphosate poisoning, managed with Aviptadil alongside conventional therapies. Despite initial challenges, including severe respiratory distress and hypoxaemia, the patient showed significant improvement following Aviptadil administration, highlighting its potential in managing Glyphosate-induced ARDS. This case underscores the importance of timely intervention and the promising role of Aviptadil in addressing the complexities of ARDS associated with Glyphosate toxicity.

Introduction

Acute Respiratory Distress Syndrome (ARDS) is a highly heterogeneous life-threatening severe form of acute respiratory failure that affects more than 3 million people globally each year, accounting for 10% of intensive care unit admissions[1]. It is characterized by an acute onset of hypoxaemia refractory to oxygen treatment and the presence of bilateral pulmonary infiltrates on the chest radiograph[2]. ARDS can arise from a variety of causes, including viral pneumonia, sepsis, trauma, cases of poisoning, and aspiration. While ARDS is a serious condition, it is not limited to any single underlying cause and can develop out of any offending agent.

Severe Glyphosate exposure can induce pulmonary inflammation, oxidative stress, and impaired lung function, which may predispose individuals to developing aspiration pneumonia that can potentially progress to ARDS. Aviptadil, a synthetic form of the vasoactive intestinal peptide (VIP), has emerged as a promising therapeutic option for ARDS due to its lung-protective properties. VIP has been shown to have anti-inflammatory, antioxidant, and bronchodilatory effects, which may help mitigate the damaging cascade of events that leads to ARDS[3]. Aviptadil has been granted Orphan Drug Designation in the United States and European Union for the treatment of ARDS[4,5], and clinical trials are ongoing to evaluate its efficacy and safety in different ARDS aetiologies. Considering all the positive inputs, here we explore a case where Aviptadil was used for ARDS resulting from Glyphosate poisoning

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Case Report

A 38-year-old male with history of adverse drug reaction presented at our hospital's emergency department having reportedly consumed 100-200 mL glyphosate insecticide concomitantly with 330 ml of beer. The patient reported to have obtained no immediate lavage after ingestion. About 3 hrs. post incident, the patient received lavage at a nearby District Hospital.

On examination, respiratory distress was evident with the patient being dyspnoeic and tachypnoeic. The patient also had erythema of the tongue and pharynx. The patient's attendants produced a container that was confirmed by the patient and hence the case was diagnosed as once of Glyphosate poisoning. The patient was advised lab investigations like CBC, CRP, Creatinine, Sodium, Potassium, LFT, ABG after admission with ECG, 2D and M-mode Echo, Chest X-Ray. Simultaneously, the patient was started on IV fluids and PPI, antiemetics and necessary adjuncts. Since Glyphosate is not a conventional organophosphorous compound and no typical signs and symptoms of organophosphorous poisoning (Op) were evident, atropinization was not attempted.

On day 2, the patient had fever as well as hypoxia. He was treated with IV paracetamol. SpO_2 was 94% with 3 L of supplemental O2 delivered via nasal prongs. The blood reports reflected increased CRP and SGPT levels. Doxycycline 100 mg IV BD and piperacillin + tazobactam (4.5 gm) IV TDS were started for the patient and ultrasonography, steam inhalation, blood for triple serology and a retake of chest X-Ray were advised. Sputum culture was posted. The patient could only speak in short phrases and could not swallow.

On day 3, with further worsening of hypoxia, the patient experienced severe distress and a P/F ratio of 102 on ABG. The patient was put on NRBM. Chest Xray demonstrated fresh infiltrates and the Chest, on auscultation was full of crackles and wheezes. Considering the critical condition of the patient, the patient was advised to be shifted to a higher center with ECMO support. ICS-LABA and Ipratropium nebulizations were deployed and Aviptadil injection's were started after counselling the patient relatives. Atropinization was attempted, despite there being no objective signs of OP poisoning. This had to be withdrawn 8 hours down the line due to hallucinations and severe delirium. Pulmonology referral was made.

On day 4, IV Hydrocortisone was started in discussion with the Pulmonologist and the patient was seen by the Gastroenterologist, who advised upper GI endoscopy.

On day 5, stool samples were sent for OBT. The patient complained of throat pain with mucous expectoration and mild dyspnoea. Upper GI endoscopy was performed under local anaesthesia and a feeding Nasogastric tube was successfully placed. The patient was advised for CECT thorax as his O2 demand had started reducing and it was possible to move him out of ICU to the CT console. Antibiotic Clindamycin 600 mg IV TDS was started along with other ongoing medications. RT feeding was started with plain water.

On day 6, the patient showed significant improvement as his O2 requirement was down to 1 – 2 LPM and he was symptomatically no longer breathless. ABG confirmed resolution of hypoxia and NG feeding could be established.

On day 7, despite some wheeze and throat discomfort, the patient kept improving and he could be weaned off supplemental oxygen, which was remarkable. Report of HRCT thorax confirmed bilateral pneumonia with mild Pleural effusions.

On day 8, nasogastric tube *in situ*, the patient was given trials of oral feeding and shifted to the Step down Unit.

On day 9, mild transaminitis was seen on LFT. Psychiatry referral was made. Oral feeding was initiated and established.

On day 10, IV antibiotics were replaced with oral medications.

By day 11, patient was discharged with advice for follow up. On digital pulse oxymetry he was maintaining 98%, while inhaling ambient air.

Discussion

Glyphosate herbicide, one of the most commonly used herbicides worldwide is generally thought to be minimally toxic to humans. However, clinical toxicologists sometimes encounter cases of severe systemic toxicity. Following oral ingestion of Glyphosate, approximately

30–36% of the compound is absorbed into the body. Peak concentrations in tissues are typically observed around 6 hours post-dosing. Glyphosate undergoes minimal metabolism and is primarily excreted unchanged in the faeces[6]. Rapid ingestion of Glyphosate can trigger airway irritation and aspiration, suggesting direct airway and respiratory tree damage in Glyphosate toxicity. Severe pulmonary damage causing hypoxaemia can impact cardiovascular function, alongside metabolic acidosis and hyperkalemia indicating organ dysfunction severity. Aspiration is well known to be a major cause of ARDS. Once aspirated, Glyphosate or other gastric contents can result in pulmonary endothelial and epithelial damage and a subsequent increase in permeability, which then progresses to ARDS[7].

Severe laryngeal injury is a key factor in respiratory aspiration and a significant contributor to morbidity/mortality in glyphosate poisoning[8]. In the context of ARDS, the therapeutic landscape is marked by a continuous search for effective treatments that can improve patient outcomes. Aviptadil's multifaceted mechanism of action sets it apart from other ARDS treatments. It has demonstrated anti-inflammatory effects, notably improving inflammatory markers such as lactate dehydrogenase, troponin, CRP, ferritin, D-Dimer, and Interleukin-6, with CRP and IL-6 showing the most substantial average per cent reduction[9]. These anti-inflammatory properties contribute to a decrease in alveolar and interstitial oedema, which can improve gas exchange and oxygenation, as indicated by enhancements in the P/F ratio[10,11]. Furthermore, Aviptadil increases pulmonary surfactant production, which is crucial for maintaining lung volume and preventing atelectrauma, thereby reducing the shunt fraction in ARDS[12].

The inhibition of alveolar epithelial cell apoptosis by Aviptadil is another key aspect of its action, helping to preserve lung tissue integrity and function. Additionally, Aviptadil mitigates ischaemia-reperfusion injury, which can exacerbate tissue damage when blood flow is restored after a period of ischaemia. These effects have been substantiated by randomized controlled trials, which showed significant positive outcomes, including high rates of decannulation and successful extubation[13].

Conclusion

This case report highlights the way of management of ARDS in Glyphosate poisoning. The findings presented in this report shed light on the potential therapeutic role of Aviptadil in addressing the challenges associated with ARDS in the context of Glyphosate poisoning.

The key takeaway from this case is that early and aggressive treatment is crucial in reducing mortality rates, particularly in the absence of a specific antidote for Glyphosate poisoning. Aviptadil, with its demonstrated ability to mitigate ischaemia-reperfusion injury, inhibit alveolar epithelial cell apoptosis, and improve respiratory function, may offer a promising approach to managing ARDS in Glyphosate poisoning cases.

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CASE REPORT

Acute Necrotizing Pancreatitis In A Young Male With Hereditary Distal Renal Tubular Acidosis

Dr. Arshad Akeel[1], Dr. Rajeev Annigeri[2], Dr. Eswer Subbaiyan[3], Dr. Joe Clinton[4]

Abstract

This case report is about a 27-year-old male with hereditary distal renal tubular acidosis (RTA) which was diagnosed in childhood due to a positive family history. He later developed acute necrotizing pancreatitis despite there being no prior risk factors. The patient had a lengthy ICU stay which led to significant complications including infections such as endocarditis. As the underlying cause of pancreatitis is not clear in this young male, genetics is thought to have played a role. This case sheds light on the potential for varied complications in patients with hereditary distal RTA and the importance of comprehensive evaluation and management.

Introduction

Distal RTA is a rare renal disorder characterized by impaired urine acidification in the distal tubules or the collecting ducts. It is typically associated with metabolic acidosis and hypokalemia. Urinary pH is usually more than 5.3. It is also associated with nephrolithiasis and nephrocalcinosis. The major causes include hereditary genetic mutations in children, whereas secondary distal RTA in adults is mostly associated with autoimmune diseases and drugs.

Case Report

This 27-year-old gentleman with a history of hereditary distal renal tubular acidosis with complaints of severe abdominal pain and vomiting was initially managed elsewhere and referred here for further management. He had a history of similar abdominal pain 6 months ago and was treated conservatively elsewhere. He was born from a 3° consanguineous marriage (the patient's father was his mother's half-uncle) (Fig. 1). While enquiring about the family history, it was found that, about 10 years ago, his elder brother was admitted for hypokalemic paralysis which was found to be due to distal RTA. There was also a family history of failure to thrive and childhood death in his second cousins. At that time, our patient was also screened and was found to have distal RTA. He has been on daily potassium supplements since then. He was not a consumer of alcohol or tobacco.

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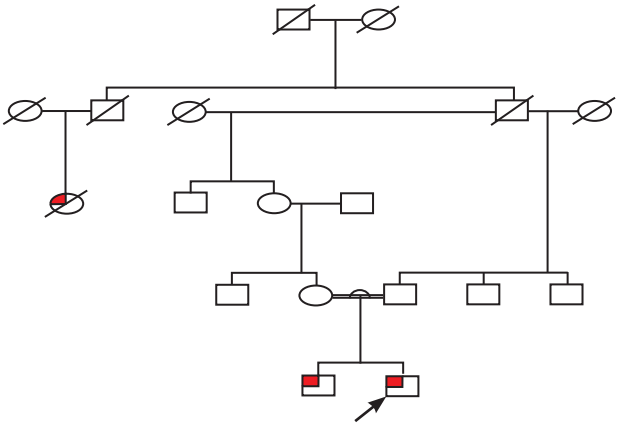

Fig. 1 Pedigree chart of the patient.

On examination, he was conscious, oriented, hypotensive and tachycardic. There was diffuse abdominal tenderness on examination. Fluid resuscitation and inotrope support were started. Basic investigations showed anaemia, leukocytosis, elevated amylase and lipase. Serum procalcitonin was high. Blood cultures sent in the prior hospital grew Klebsiella pneumonia. He was started on empirical IV antibiotics. Computed tomography of the abdomen with contrast (CECT abdomen) was suggestive of acute necrotizing pancreatitis with peripancreatic fluid collection (Fig. 2). His calcium and triglyceride levels were within normal limits. percutaneous drainage was deemed not feasible due to gross bowel dilatation and a high chance of bowel injury. Laparoscopic drainage and washing were carried out and a pus culture sent from the collection also grew *Klebsiella pneumonia*. IV antibiotics were fine-tuned as per the sensitivity report. He required intermittent inotropic support. Repeat CECT abdomen was done due to persistent pain and elevated WBC count which showed residual collection. Percutaneous drainage was done. He required multiple blood products. Repeat blood culture grew Trichosporon and he was started on Amphotericin B and Voriconazole. He grew increasingly drowsy and also developed hypotension. Inotropes were re-started and antibiotics were escalated. His Antinuclear Antibody and Extractable Nuclear Antigen profiles were negative.

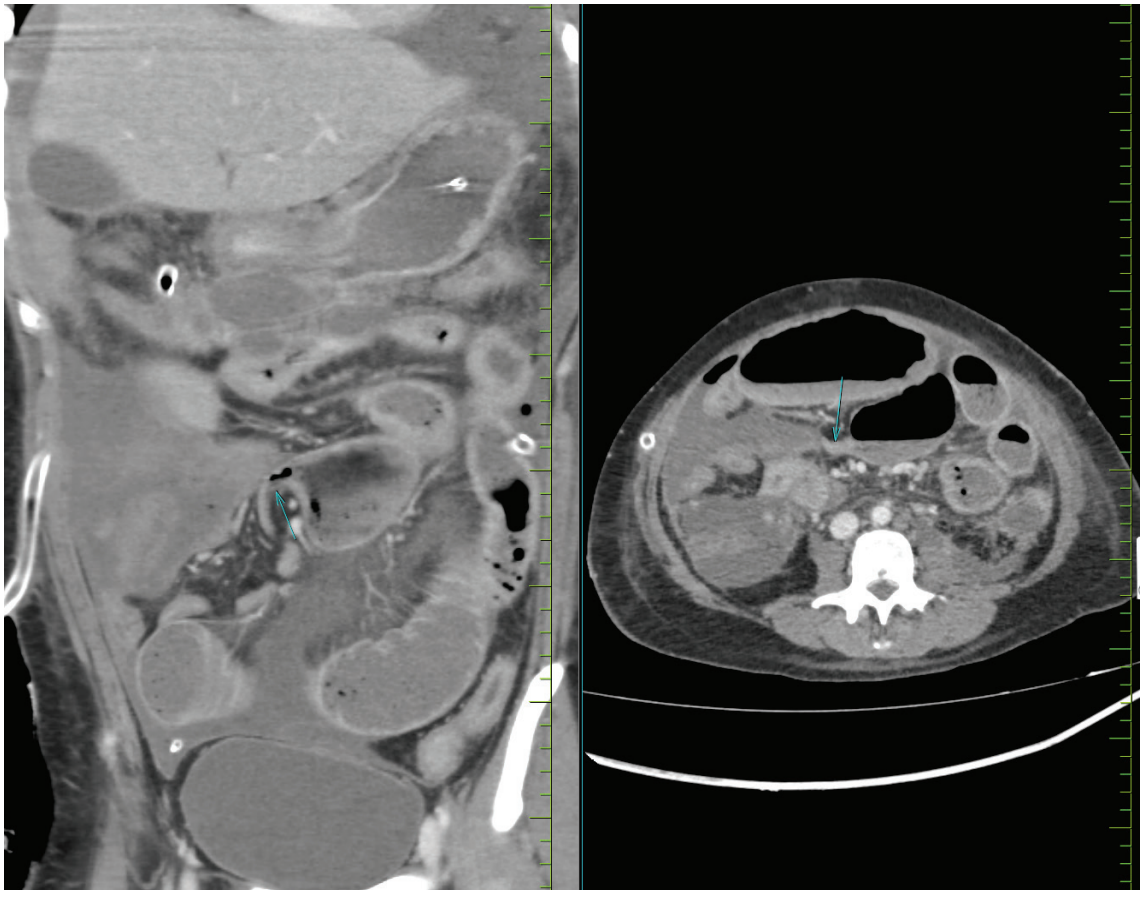

Fig. 2 CECT abdomen showing necrotizing pancreatitis and peripancreatic collection

He was intubated due to a drop in Glasgow Coma Scale below 8. His blood cultures also grew *Candida krusei.* An emergency laparotomy was done to drain peripancreatic infective collections, and peripancreatic necrotic tissue was removed and sent for culture and histopathology. A perforation in the small bowel was noted which was exteriorized in the midline and loose closure of the abdomen was done. A relook laparotomy was done after 2 days, clots were removed, a 10-15 cm segment of small bowel was resected and a double barrel stoma was created. *Candida krusei* was persistent in blood culture. Resected tissue cultures grew Carbapenemase-resistant Klebsiella and *Enterococcus faecium.* He also had intermittent fever spikes.

Repeat CECT abdomen was suggestive of a pseudoaneurysm, likely arising from one of the terminal mesenteric branches of the ileocolic branch of the superior mesenteric artery, with leak resulting in a large haematoma, surrounding and compressing the caecum which was promptly embolized (Fig. 3). Transoesophageal echocardiography was done due to persistent fungaemia which showed an 8 mm strand-like vegetation over the aortic valve suggestive of infective endocarditis probably due to Candida and anti-fungals were continued. He had spontaneous fresh bleed from the drains leading to hypotension and his inotropic requirement increased. After a total stay of about 30 days, he had worsening metabolic acidosis, hypoxemia and impaired renal function and expired despite adequate resuscitation efforts.

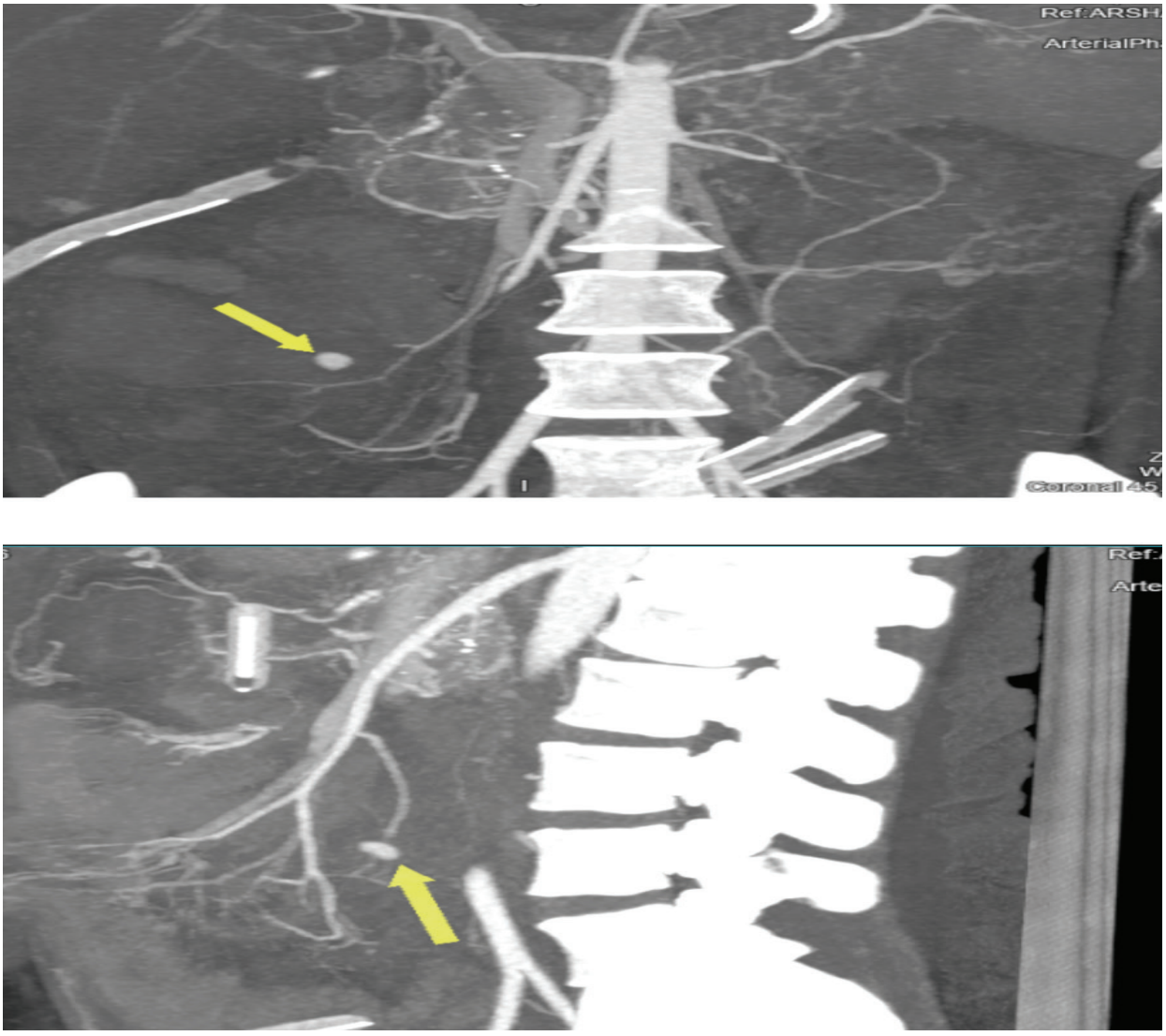

Fig. 3 A pseudoaneurysm in the CECT abdomen

Discussion

Distal or type 1 RTA is a rare condition characterized by the kidney's inability to properly acidify urine in the distal tubule and collecting ducts, leading to hyperchloremic metabolic acidosis with a normal anion gap. It is often accompanied by hypokalemia[1]. The most common cause for distal RTA varies in children and adults. Distal RTA in adults is usually secondary to autoimmune disorders such as Sjogren's syndrome, systemic lupus erythematosus and drugs such as Ifosfamide and Amphotericin B[2]. In children, hereditary factors, particularly mutations in the SLC4A1, ATP6V0A4, and ATP6V1B1 genes, form the major cause. SLC4A1 encodes a protein in the basolateral chloride-bicarbonate exchanger, while ATP6V0A4 and ATP6V1B1 code for proteins in the apical hydrogen-ATPase. Mutations in SLC4A1 follow an autosomal dominant pattern, whereas mutations in ATP6V1B1 and ATP6V0A4 genes are inherited in an autosomal recessive manner[1]. The resulting hypokalemia, stemming from renal potassium wasting, can lead to severe consequences, including muscle paralysis and respiratory arrest[3].

In contrast, acute pancreatitis, which is inflammation of the pancreas, typically arises from causes such as gallstones and chronic alcohol use. Gallstones remain the most common cause of pancreatitis. Obstruction of the ampulla plays a major role in gallstone-induced acute pancreatitis. Chronic alcohol use is thought to injure the pancreas through lysosomal enzymes. The majority of cases involve acute interstitial oedematous pancreatitis, while a smaller subset progresses to necrotizing pancreatitis with extensive tissue necrosis. Acute pancreatitis carries a 5% overall mortality, which escalates to 17% in necrotizing pancreatitis[4]. Necrotizing pancreatitis results in vascular leak syndrome leading to increased third space fluid losses and worsening of pancreatic hypoperfusion. The initial 48 hours are critical, with intravenous hydration proving to be the most effective treatment[5]. However, acute pancreatitis has not conventionally been associated with distal RTA.

The puzzling aspect of this case was the development of acute necrotizing pancreatitis in a healthy patient with hereditary distal RTA. Common aetiological factors for pancreatitis, such as gallstones, chronic alcohol use and hypertriglyceridemia were absent. The lack of genetic testing in this patient introduces the possibility of an underlying genetic defect predisposing him to pancreatitis. Alternatively, the coexistence of Sjogren's disease, which has been associated with an increased incidence of pancreatitis, could be considered[6]. However, the patient's negative autoimmune workup and the early onset of distal RTA in childhood, where genetic mutations are the primary cause, make the latter scenario less likely.

The possible connection between distal RTA and acute pancreatitis underscores the complexity of rare genetic disorders and the potential for diverse clinical manifestations. This case prompts the need for further research into the potential genetic links between distal RTA and pancreatitis emphasizing the importance of personalized and comprehensive medical approaches in managing these intricate medical conditions.

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CASE REPORT

Vitamin B12 Deficiency Presenting As Psycosis Without Neurological Manifestations

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Abstract:

Cobalamine deficiency is a common disorder and generally presents as megaloblastic anaemia and subacute combined disorder of spinal cord. This presentation is a case of cobalamine deficiency without anaemia or subacute combined degeneration of spinal cord; rather solely as psycosis responding to cobalamine treatment.

Introduction

Cobalamine exsists in a number of different chemical forms ; all have a Cobalt atom at the centre of corin ring connected to ribonucleotide through an aminopropanol bridge. Vitamin B12 or Cobalamin is a cofactor in folate coenzyme recycling, where it acts as a methyldonor and helps in myelination. This also play a significant role in DNA synthesis in RBC. Vitamin B12 is needed for integrity of myelin. The main pathological finding is focal demyelination affecting the spinal cord, with B12 deficiency as also lesion in peripheral nerves, optic nerves and cerebrum. Advanced neurological disease due to vitamin B12 deficiency is now rarely seen in the developed world. Vitamin B12 is synthesized by colonic bacteria and its deficiency is seen in alcoholic subjects, after bowel surgery, insufficient intake from diet especially pure vegan diet (although rare but documented in some studies), malabsorption from pernicious anaemia, gastritis, pancreatic insufficiency, Small Instestinal Bacterial Overgrowth, drugs e.g., prolonged used of PPI, neomycin, metformin etc. fortification of food with folic acid often masks the slow neurological manifestations of vitamin B12 deficiency. Macrocytic anaemia, megaloblastic anaemia, subacute combined degeneration of spinal cord, peripheral neuropathy, dementia, neuropyschiatric manifestation have been reported in patients with vitamin B12 deficiency.

Case Presentation

A 32-year old male vegan patient, Engineer By profession, was brought by relatives for his irrelevant talk. He would talk to himself and to imaginary things. His nature became very suspicious and he would doubt everything. His friend noticed that of late he was becoming more and more suspicious. He was often found talking to himself. He was able to walk and to do all physicial activities as usual. On detailed questioning it was found that the behavioural changes were insidious in onset and were noticed in past few months but now became more and more pronounced. He was found to be getting abusive in addition to his suspicious behaviour. He was having history of hypertension

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and was on telmisartan 40 mg with amlodipine 5 mg since the past 2 years. He smoked 4 cigarettes per day. A non alcoholic, he was not on any illicit drugs. There was no history of any other comorbid risk condition nor was he on any other medicine. he was married and was working as a marketing agent. His mother had hypertension and lumbar disc disease and father had type 2 diabetes. His main concern was that he was having auditory and visual illusions and he was aware this was something unusual. He was brought by his close friend and family members as his behaviour was getting worse and was causing them a lot of social embarrassement. They took him to a psychiatrist, who, after taking his history labelled him as having acute psycosis as early manifestation of schizophrenia. There were no other complaints.

On examination

Pulse was 78/ min, BP 140/ 82 mm Hg, no pallor, no icterus, no cyanosis, no oedema, no clubbing, CVS – S1 S2 normal no S3 S4; RS – vesicular type, no crepitation, no added breath sounds; PA – soft, no lump, no hepatosplenomegaly found; NS – motor power normal, Romberg's negative, coordination in both upper and lower limbs normal, joint position sense normal, vibration sense normal, no nuchal rigidity. DTRs upper – 1+ biceps, triceps, supinator. lower limb –1+ knee and 1+ ankle after reinforcement, plantars downgoing.

Investigation

Full blood count with liver function tests, thyroid function tests, renal function tests, urine for toxicological test, HbA1c, vitamin B12, RBC folate, urine routine, CT brain, electrolytes and calcium, magnesium, EEG, ECG were performed. xray chest PA view was also done.

WBC revelead TIC of 4,100/cumm, Hb 10.8 g/l, N 4 *10 ^ 9/ lit, lym 3*10 ^ 9 / lit mcv 118 fl/lit, mch 33 pg/lit, Na 134 mmol/l, K^+ 4.2 mmol/lit, creatinine 80 micromol/l, magnesium 0.9 mmol/l, corrected calcium 2.4 mmol/l. CT brain unremarkable, EEG reported, normal urine negative for toxicological screen, serum B12 12 ng/lit, RBC folate 220 ng/l, anti intrinsic factor AB-negative, rest of the reports were within normal reference range

Treatment

He was started on parenteral vitamin B12 1000 meg/ per day intra-muscular for 10 days, followed by a bi-weekly dose for the next 4 weeks and thereafter weekly for the next 8 weeks and now once monthly dose. He was started on haloperidol tab. 5 mg two times a day for 10 days as he was experiencing hallucinations along with oral B-comple, thereafter on prn basis haloperidol was given. Patient was asked for repeat psychiatric and psychologist assessment as he was not on any psycotropic drugs but the team monitored the response.

Outcome and follow-up

Patient was followed-up at 10 days and after every fortnight. After 20 days the patient did not require the dose of haloperidol and his behaviour markedly improved. After 6 weeks patient recovered completely, and even the family members and friend did not notice any abnormal behaviour. He resumed his routine work, and after 6 months the patient was not only stable but continued to improved equally in the psychiatrists review as well. Thereafter, no psychotic symptoms were reported

Discussion

This case study is unique because it is well known that vitamin B12 deficiency presents 95% megaloblastic anaemia and neuropsychiatric manifestations as described above, but vitamin B12 deficiency presenting solely as psycosis is rare manifestation. This reminds us of organic aetiology of psychiatric cause before labelling patient as functional disorder. As this patient was well educated and was in a marketing job and gradual worsening of behaviours and increased suspiciousness and later coming up with audio-visual hallucinations made him consult a psychiatrist. Later medical evaluation found him to be haveing deficiency of vitamin B12, to which he significantly improved after treatment with vitamin B12.

Conclusion

Vitamin B12 deficiency can presents solely as psychiatric manifestation without significant neurological or haematological presentation.

Learning Points

From the case study it reminds us that whenever any psychiatric presentation presents to a physician, it is imperative to rule out organic pathology behind such manifestation that can be treated or prevented. functional or cryptogenic aetiology should only be labelled when all the know or identifiable organic cause are ruled out.

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PICTURE MEDICINE

Systemic Sclerosis

Nishat Anjum[1], Kaushik Ghosh[2]

A 25 year old female patient came to the OPD presenting with bilateral digital pitted scarring, non-healing digital ulcers, dry gangrene (Fig. B), prominent calcinosis cutis (Fig. C), pursed lip and puckered mouth (Fig. A). She complained of mild arthralgia, dysphagia, and tightening of facial skin and hands. On examination, there was thickening of nails with fibrotic build-up over nail beds (Fig. D). The patient exhibited a positive Allen's Test. Her presentation was consistent with CREST syndrome (Calcinosis cutis, Raynaud's phenomenon, Esophageal hypomotility, Sclerodactyly, and Telangiectasia). Her chest X-ray and 2-D Echocardiography were unremarkable; she tested positive for anti-centromere antibodies. Given the long-standing history of skin fibrosis without any systemic involvement, a diagnosis of Limited Cutaneous Systemic Sclerosis (SSc) was made. She was treated with oral nifedipine and nitroglycerine ointment for local application.

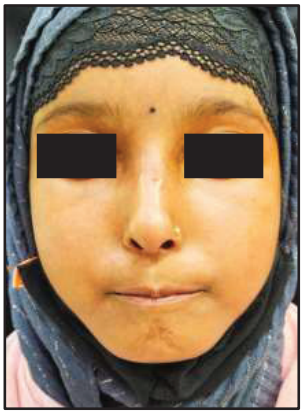

Fig. A

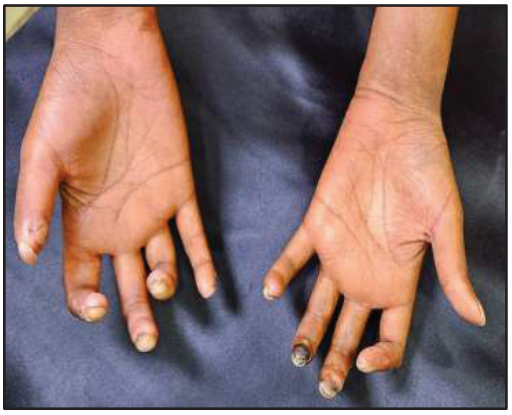

Fig. B

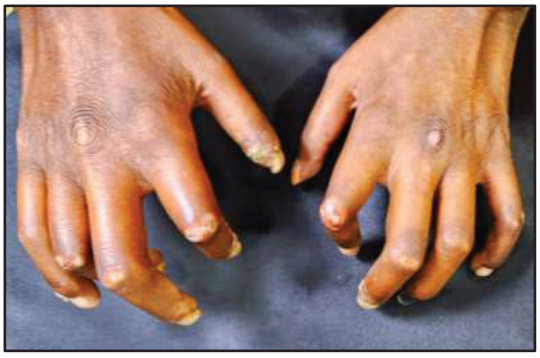

Fig. C

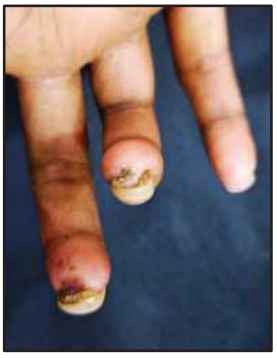

Fig. D

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Answers

1. **Describe the ECG finding.**
   Irregular rhythm. Wide bizarre discordant QRS complex without preceding P wave after every two sinus QRS complexes. There is a pause after every bizarre complex. The bizarre QRS morphology is LBBB type in precordial leads and it's positive in II, III, aVF, and negative in aVR.

2. **Which is the ECG diagnosis?**
   Ventricular trigeminy with the origin of VPCs from the Right Ventricular Outflow Tract.

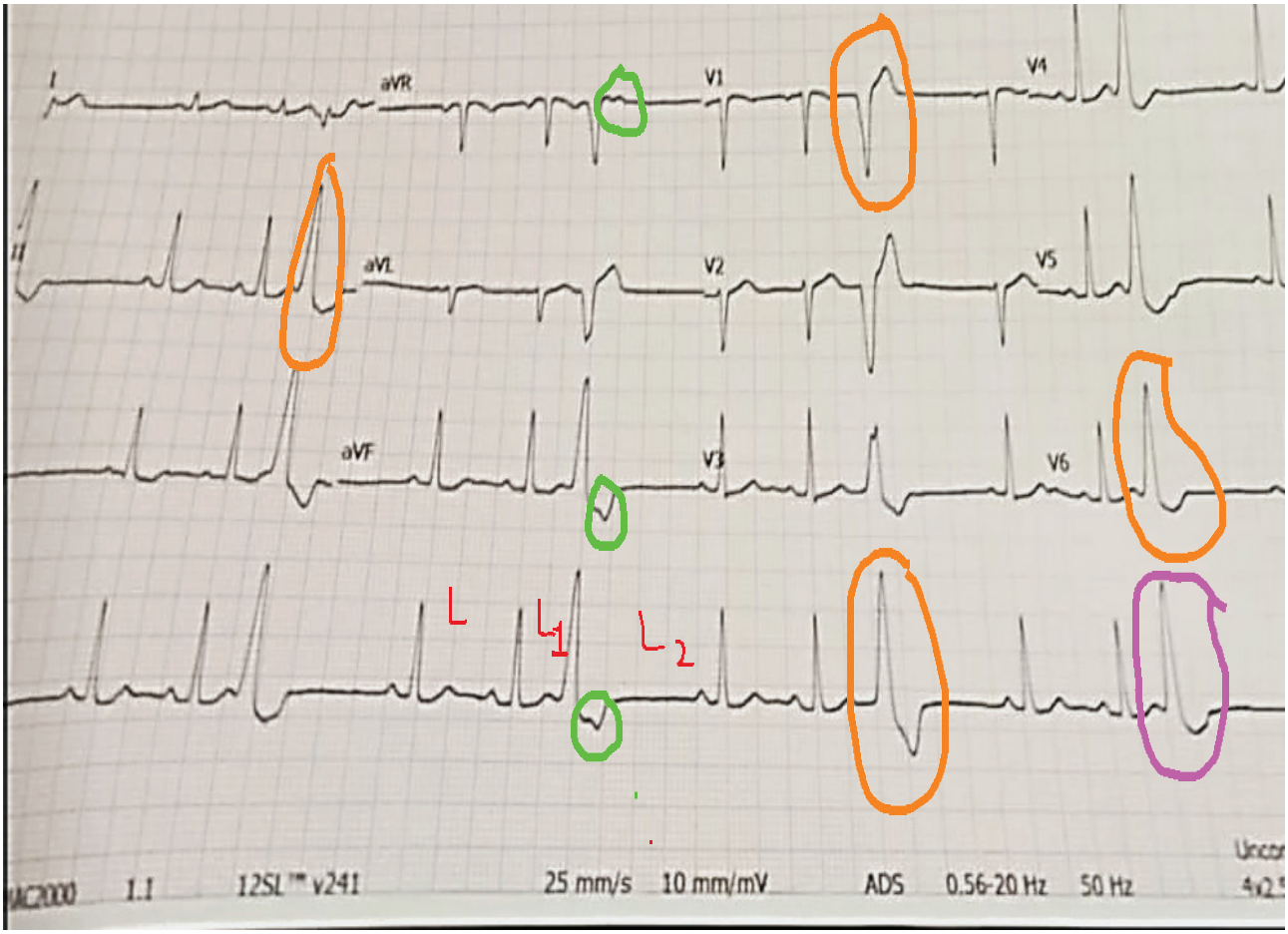
3. **Justify your answer.**
   Wide bizarre discordant QRS complex without preceding P wave (Ventricular origin) after every two sinus QRS complexes (Trigeminy). There is a pause after every bizarre complex without resetting (Post ectopic compensatory pause, L1+L2=2L). The bizarre QRS morphology is LBBB type in precordial leads (RV origin) and it's positive in II, III, aVF, and negative in aVR (Axis is from above downwards, i.e. from outflow tract).

4. **What is the initial management?**
   Beta-blocker.

SPECIAL FEATURES:

R on T (Pink marked) – high risk feature.

Retrograde (from below upwards) V to A conduction causing P wave just after VPC which is positive in aVR but negative in inferior leads (green marked).



Answers

1. **What is the possible diagnosis of this lady?**
   Infective Endocarditis involving the mitral valve.

2. **Which diagnostic criteria is followed to establish the diagnosis?**
   Modified Duke Criteria.

3. **What are the types of PUO?**
   Classic PUO, Nosocomial PUO, Neutropenic PUO, HIV associated PUO.

4. **What are the common possible complications of this disease?**
   Local complications (abscess, tissue destruction), Metastatic complications (Embolism, organ abscess), Immune complex mediated complications (Glomerulonephritis, Osler's node, RF+ve, Roth spot)

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