LETTER TO THE EDITOR

An Unusual Case of Pancytopenia: The Lessons Learnt

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Abstract

Pancytopenia is a common hematological abnormality encountered in clinical practice. We here report a 36-year-old male who presented to emergency department with complaints of weakness of bilateral lower limbs, burning sensation in all four limbs with history of loose stools, and vomiting 5 days back. The complete blood count of patient showed pancytopenia with no circulating atypical cells. Bone marrow examination performed showed nonspecific but characteristic findings. After excluding the possibility of infective etiology, a possibility of heavy metal toxicity was suspected in multidisciplinary meeting. The urine and blood levels of arsenic done came out very high, and a diagnosis of arsenic poisoning was made. Patient had multisystemic involvement with features characteristic of arsenic poisoning. The present case was a diagnostic challenge in face of nonforthcoming history. This case beautifully highlighted the importance of multidepartmental approach in such cases to arrive at unerring diagnosis and the unique bone marrow findings, although nonspecific were sufficient enough to indicate the possibility of acute insult to the hematopoiesis.

Keywords: Abnormal megakaryocytes, Arsenic poisoning, Erythroid dysplasia.

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Introduction

Pancytopenia is a common hematological abnormality encountered in clinical practice. The pancytopenia can result from various conditions, and the workup requires obtaining detailed clinical details and extensive investigations, including bone marrow examination. The common conditions associated with pancytopenia are bone marrow failure syndromes, marrow infiltrative lesions, peripheral destruction of hematopoietic cells, autoimmune disorders, infections, and ineffective hematopoiesis. Acute arsenic poisoning is a very rare cause of pancytopenia, seldom encountered in the clinical practice. In the absence of apparent history of exposure to arsenic, the diagnosis of acute arsenic poisoning is challenging. There is only limited literature available describing peripheral blood and bone marrow changes in cases of acute arsenic poisoning. We here report a case of acute arsenic poisoning and unique clinical and laboratory features that helped us in reaching the right diagnosis.

Case Description

We here report a 36-year-old male who visited emergency department with complaints of weakness of bilateral lower limbs, burning sensation in all four limbs with history of loose stools, and vomiting 5 days back. There was no history of fever, neck stiffness, or rashes. Patient was conscious and on examination had initial pulse rate of 146 per minute and blood pressure of 90 per 66 mm Hg. There was no lymphadenopathy or organomegaly. Neurological examination showed 4+/5 power in both lower limbs and 5/5 in both upper limbs. Neurology consultation was taken, and possibility of Guillain-Barre syndrome (GBS) vs weakness due to hypokalemia (2.6 mEq/L) was initially suggested. Nerve conduction velocity studies were normal. Baseline laboratory investigations showed elevated levels of hepatic enzymes (aspartate aminotransferase—197.7 IU/L, alanine transaminase—281.0 IU/L, and gamma-glutamyl transferase—581.1 IU/L), hypocalcemia (7 mg/dL), and hypoalbuminemia (2.7 g/dL). At presentation, serum sodium, chloride, creatinine, urea, total creatine phosphokinase, magnesium, and phosphorus levels were within normal limits. There was mild prolongation of prothrombin time and activated partial thromboplastin time. The patient was nonreactive for hepatitis A virus, hepatitis E virus, hepatitis B virus, hepatitis C virus, and human immunodeficiency virus. The thyroid function tests were within normal limits. The complete blood counts showed pancytopenia (Hb—11.1 g/dL, total leukocyte count—0.7 $\times$ 10^9/L, absolute neutrophil count—0.3 $\times$ 10^9/L, platelet count—9 $\times$ 10^9/L), for which bone marrow aspiration and biopsy were done. The physician who did bone marrow aspiration described that blood flowed out of the bone marrow aspiration needle hub as soon as needle was inserted into the marrow cavity, an unusual finding during bone marrow procedure. This finding later correlated with increased vascularity

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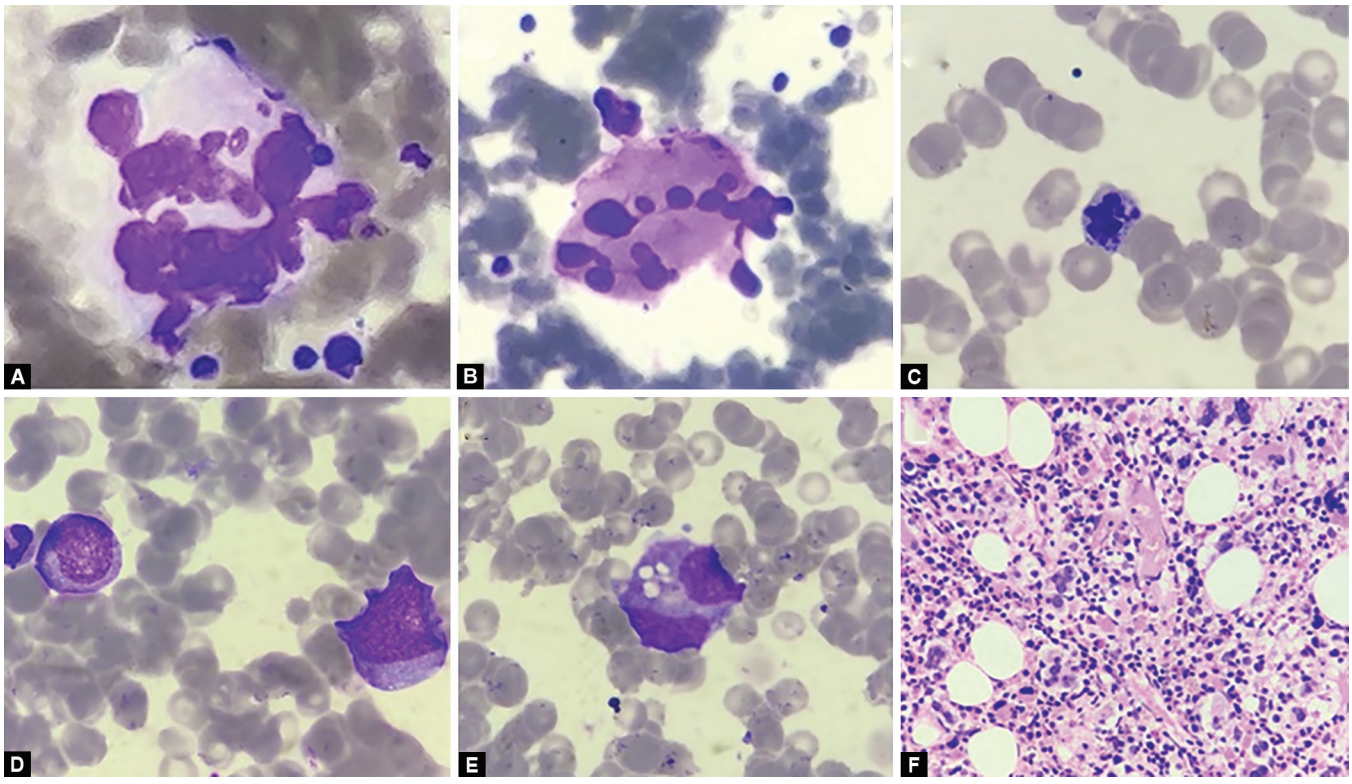
and vasodilatation on the bone marrow biopsy. The bone marrow examination showed a significant number of megakaryocytes with large hyperlobated and deeply lobated nuclei (Fig. 1). The erythroid and granulocytic lineages showed maturational shift to left with predominance of early precursors. The cells in erythroid lineage were predominantly early precursors (proerythroblasts, early erythroblasts, and early intermediate erythroblasts), and the occasional late erythroblasts seen show bizarre nuclear shapes and karyorrhexis accompanied by basophilic stippling (Fig. 1C). The cells of granulocytic lineage showed prominent granulation, occasional neutrophil with lobe separation, and myelocytes with persistent cytoplasmic basophilia (Figs 1D and E). There were no atypical cells in the bone marrow aspirate, and eosinophilic lineage was relatively preserved. The bone marrow biopsy showed extensive congested vascular channels with extravasation of red blood cells (RBCs). There was significant megakaryocytic hyperplasia with many megakaryocytes showing large darkly stained hyperlobated nuclei (F). Based on peripheral blood and bone marrow findings, possibility of acute severe insult to marrow was suspected. During the course of next 3 days, patient developed fever, morbilliform rash over flanks and thigh, and delirious behavior. Magnetic resonance imaging of the brain was done which showed diffuse mild gyral thickening. Cerebrospinal fluid examination done was normal. Patient had multiple episodes of polymorphic ventricular tachycardia (pVT) (with very low arterial pressure), which was cardioverted repeatedly by defibrillation of 200 J. Patient went into hypotension requiring inotropic support and drop in left ventricular ejection fraction (LFEF) to 28%. Patient progressed to quadriparesis with 0/5 power in both upper and lower limbs. He also started having raised serum creatinine. Case was discussed in multidisciplinary meeting, and multiple differential diagnoses were considered, including heavy metal poisoning and disseminated viral infections like dengue. On complete evaluation, arsenic blood level came out as 276.48 µg per L and arsenic random urine level was 22324.50 µg per L. Hence, the diagnosis of arsenic poisoning was made with manifestations of cytopenias, corrected QT interval (QTc) prolongation (Fig. 2), and with pVT (Fig. 3), central nervous system, and peripheral nervous system involvement. He was started on injection of British anti-lewisite (BAL) at a dose of 3 mg per kg IM every 6th hour. He had undergone hemodialysis once in view of acute kidney injury and normalized on Day 1 postdialysis. Subsequently, inotropes were stopped, and patient became fully conscious and oriented, shock recovered, liver enzymes normalized, and blood counts recovered. He was tracheostomized in view of quadriplegia with poor respiratory effort and possible prolonged ventilation requirement. Gradually, the patient was given T piece trials with on and off ventilator support and bilevel positive airway pressure support, and was slowly weaned off from noninvasive ventilator support. He started maintaining oxygen saturation at room air. His echo showed LFEF 57% suggesting recovery of



Figs 1A to F: (A and B) The megakaryocytes were abnormally large and hyperlobated (original magnification × 200, May Grunwald Giemsa); (C) The late erythroblasts showing nuclear karyorrhexis and basophilic stippling (original magnification × 1000, May Grunwald Giemsa); (D) Relative predominance of myelocytes was noted in the bone marrow (original magnification × 1000, May Grunwald Giemsa); (E) The neutrophilic precursor with lobe separation (original magnification × 1000, May Grunwald Giemsa); (F) Bone marrow biopsy showing numerous megakaryocytes and vasodilatation (original magnification × 1000, hematoxylin and eosin)

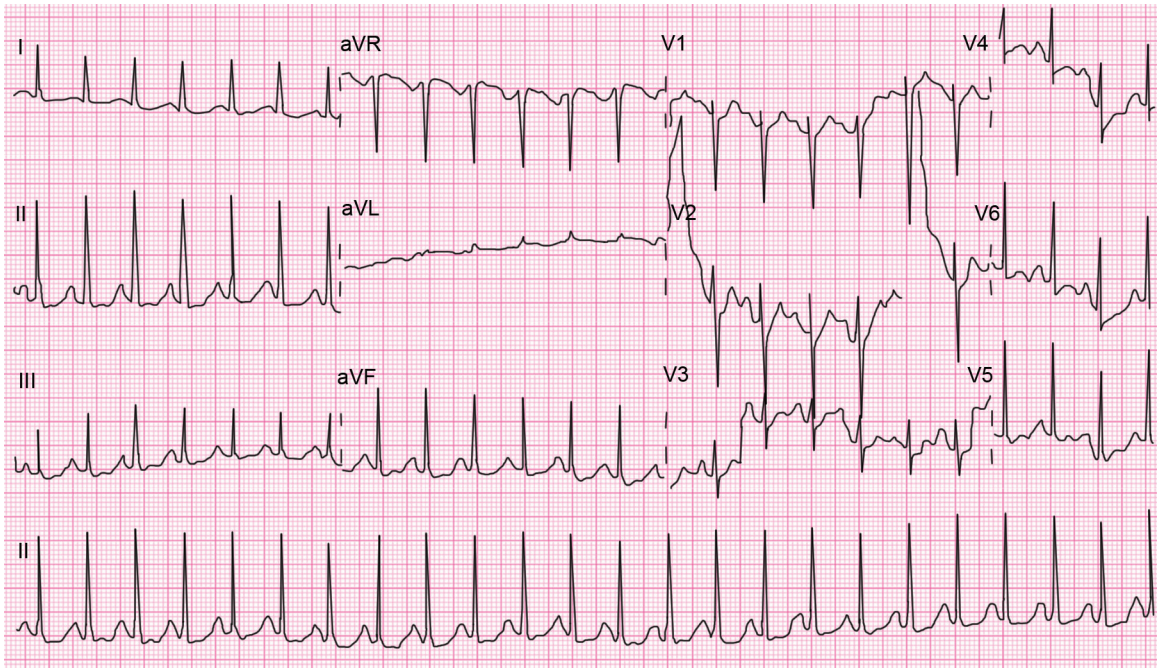


Fig. 2: ECG showing QTc prolongation

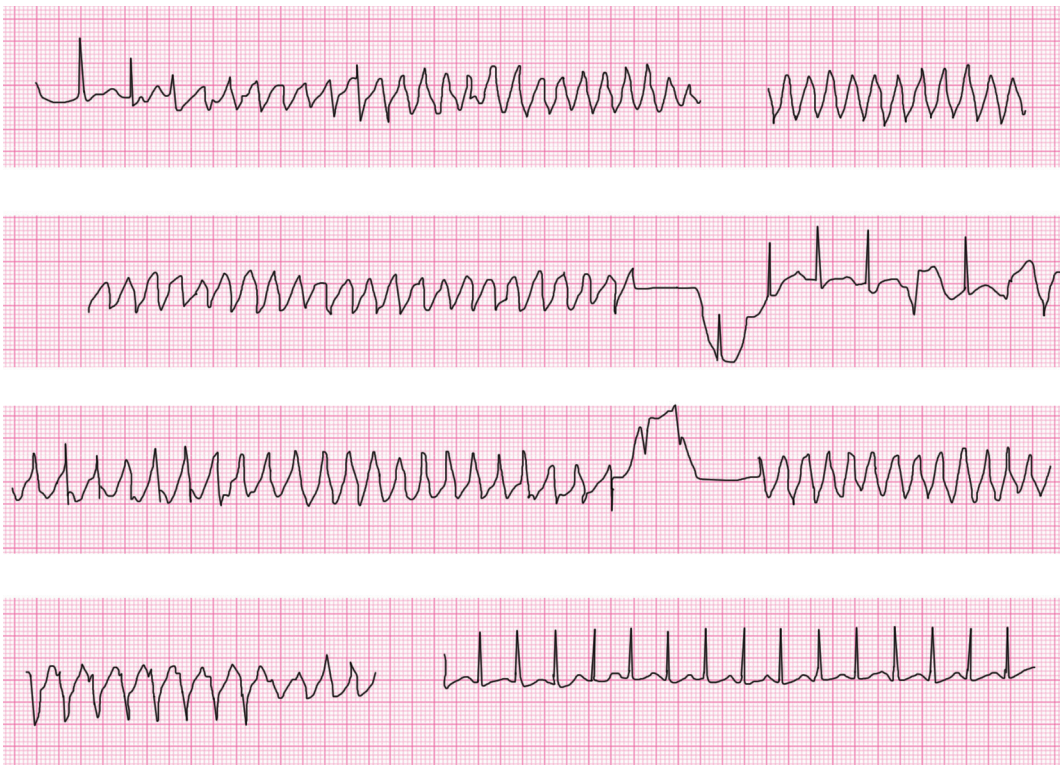


Fig. 3: Polymorphic ventricular tachycardia

arsenic-induced cardiomyopathy. His 24-hour urine arsenic level repeated was 32.31 µg per L; hence, BAL was stopped.

He was afebrile, off inotropes, maintaining hemodynamics, and maintaining oxygen saturation on room air. His power of the upper limb (proximal—2/5 and distal—0/5) and lower limb (proximal—2/5 and distal—0/5) had improved. His attendants took him to some another hospital for further supportive care and rehabilitation. Subsequently, he was lost to follow-up.

Discussion

Arsenic poisoning in India largely results from contamination of drinking water, resulting in mostly chronic arsenic toxicity. The

other less common causes of arsenic poisoning include accidental exposure to arsenic containing substances, like insecticides, pesticides, herbicides, paints, and wood preservatives, and these patients usually present as a case of acute arsenic poisoning. Arsenic has also been used as a homicidal agent. In cases with absent forthcoming relevant clinical history suggestive of arsenic toxicity, diagnosing cases of an acute arsenic toxicity is extremely challenging because of highly varied and multifaceted clinical presentation.

The gastrointestinal (GI) manifestations are usually characteristic in a case of acute arsenic poisoning. In the present case, patient gave history of loose stools and vomiting 5 days back, but doesn't complain of diarrhea at the time of admission, which was unusual for acute arsenic toxicity. The diarrhea in arsenic toxicity is mainly attributed by increased vascular permeability resulting in extravasation of RBCs in the gut, reason for the typical gross features, described as "bloody rice water" diarrhea. Interestingly, the bone marrow biopsy in the present case also showed marked vasodilatation and extravasation of RBCs, hereby suggesting that arsenic toxicity causes systemic vasodilatation and increased permeability, similar to that seen in GI tract.

One of the differentiating features of acute arsenic poisoning in comparison with other heavy metal toxicities is the QTc prolongation which can lead to pVT. A prolonged QTc in any patient with multisystem manifestations especially with GI symptoms should always raise the possibility of acute arsenic poisoning.[1] Acute arsenic poisoning should also be figured in the differential diagnosis of acute noninfective diarrheas, cases of acute onset-altered consciousness without definitive cause, and as a differential diagnosis in cases of suspected GBS with nonclassical manifestations along with systemic manifestations and not responding to GBS treatment.[2] The peripheral neuropathy, as seen in the present case, is common in arsenic toxicity and can mimic GBS clinically.[3]

The presence of bicytopenia and acute onset of illness prompted clinicians to perform bone marrow aspiration to rule out hematological malignancies, like acute leukemia. The peripheral blood and bone aspiration findings were striking in the present case. The bone marrow exhibited the relative maturation arrest with predominance of precursor cells, nuclear karyorrhexis and basophilic stippling in late erythroblasts, and typical megakaryocyte morphology in the form of numerous large and hyperlobated megakaryocytes. The increased proliferation and abnormal morphology of megakaryocytes may mimic myeloproliferative neoplasms (MPNs), but reduction of neutrophilic and erythroid lineages, presence of peripheral blood cytopenias, and acute onset of symptoms are inconsistent with diagnosis of MPN. These morphological changes are quite characteristics of acute arsenic toxicity, however not pathognomic, and similar hematological findings, as in our case, have been reported previously in the literature.[4–6] Thus, bone marrow findings can prove useful in cases with suspected cases of acute arsenic toxicity.

In present case, the late erythroid precursors were relatively few as compared to previously reported cases of arsenic poisoning where frequent megaloblastic erythroid precursors have been reported in the bone marrow. The possible explanation for this discrepancy might be due to acute arsenic exposure in our case as compared to more prolonged exposure of arsenic in the previously reported cases of arsenic poisoning.[7]

The rapid diagnosis is crucial as various antidotes, like dimercaprol (BAL), 2,3-dimercaptopropanesulphonate sodium, and meso-2,3-dimercaptosuccinic acid, are available as effective treatment options for this rare condition and can potentially save the life of the patient.[8] In this case, BAL was used due to lack of availability of other antidotes and also because of ease of administration of BAL in the form of intramuscular injections especially in a patient with altered consciousness.

Diagnosing acute arsenic toxicity is challenging, particularly in cases without relevant clinical history or unusual presentation. An index of suspicion, multidisciplinary approach is needed to arrive at correct diagnosis. Needless to say that correct and quick diagnosis is absolutely critical in managing cases with acute arsenic toxicity.

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