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Case Report

Linezolid induced acute toxic leukoencephalopathy and severe thrombocytopenia presenting as stroke mimic—a case report

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Abstract

A 67-year-old lady was admitted with, right sided weakness and right arm shaking. She had recently completed a course of Linezolid for a diabetic foot infection and osteomyelitis. Prior to this she had prodromal symptoms including lethargy and loss of appetite. Clinical features prompting presentation included global weakness, verbal dysfluency and visual disturbance. MRI brain showed bilateral alteration of signal in the deep white matter of the posterior frontal and parietal lobes, sparing the superficial cortical areas. These areas showed diffusion restriction, suggestive of, but not limited to, ischaemic stroke. During admission she had a decline in consciousness and was hypertensive. An acute drop in haemoglobin and platelets occurred prompting consideration of Thrombotic Microangiopathy and other drug related/malignant/infective aetiologies. A diagnosis of Linezolid induced Acute Toxic Leukoencephalopathy and thrombocytopenia was made based on clinico-radiographic features and exclusion of other causes.

Keywords: linezolid; acute toxic leukoencephalopathy; thrombotic thrombocytopenic purpura

Introduction

Acute focal neurology can have a multitude of differentials and diffusion restriction on neuroimaging points towards ischaemic stroke as a possible cause. The nature of diffuse restriction and atypical clinical features may broaden the differential to include inflammatory, infective, malignant, toxic and drug induced aetiologies. The combination of an acute anaemia and thrombocytopenia means Thrombotic Microangiopathy (TMA) needs urgent consideration as immediate treatment influences prognosis. The presence of neurological dysfunction suggests TTP, as a cause of TMA, needs evaluation.

Toxic leukoencephalopathy is a rare diagnosis to be considered in the setting of acute confusion and bilateral diffusion restriction on MR imaging; and may be secondary to certain drugs, such as Linezolid [1, 2].

The term leukoencephalopathy encompasses any disorder causing structural alteration of white matter. It may be due to genetic mutations or acquired manifestations of vascular, inflammatory, infectious, traumatic, toxic, nutritional or neoplastic disease. It produces symptoms and signs attributed directly to disruption of white matter fibres. Imaging can reveal an increase in diffusion weighted imaging with decrease in Apparent Diffusion Coefficient (ADC) values in the white matter suggesting restricted diffusion. These include toxic leukoencephalopathy, hypoxic-ischaemic encephalopathy and congenital genetic disorders.

Linezolid induced thrombocytopenia has been described in the past [3] but we present a case where exclusion of other aetiologies and some characteristic findings mean that Linezolid is the likely cause to account for our patients neurological and haematological pathology.

Case report

A 67-year-old lady was admitted with confusion, right sided weakness and right arm shaking.

Comorbidities included a duodenal ulcer, diabetes mellitus and hypertension, but importantly no prior personal or family history of neurological disorders or cerebrovascular events. Medications included Metformin, Ramipril and Lansoprazole.

She was also suffering from a non-healing ulcer on her left 5th toe. Bone fragments grew Enterococcus and Proteus. Skin swabs grew *Staphylococcus Aureus*. Osteomyelitis of the 4th and 5th metatarsals was suspected. As co-existing cellulitis not responded

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to co-amoxiclav, the patient was switched to Linezolid 600 mg twice daily was commenced for four weeks. Full Blood Count after 3 weeks of treatment with Linezolid showed Hb 104 g/L, WCC 6.1 ×10 9/L, platelets 119 ×10 9/L and MCV 85 fL. Her platelet count was last checked three years prior and was within normal range at 245 ×10 9/L. She finished her full five-week course of linezolid to which her osteomyelitis responded well.

Two days after the last dose of Linezolid she noticed right arm shaking and weakness.

Admission blood pressure was 189/63. Her Glasgow Coma Scale (GCS) was 14/15 (E3, V5, M6). She had mild global weakness and was unable to finger count. However, she had power of 4/4 in all limbs, normal tone and plantar responses were flexor. There was evidence of right sided neglect.

CT head was unremarkable. Her haemoglobin (Hb) was 69 g/L, but white cell count (WCC) and platelets were within normal limits. On admission, aspirin was given while a MRI Head was requested to investigate the considered differentials, including progressive multifocal leukoencephalopathy, Posterior Reversible Encephalopathy Syndrome, and encephalitis.

She developed a progressive decline in consciousness in the next 24 h. MRI Head revealed bilateral alteration of signal seen within the deep white matter of the posterior frontal and parietal lobes. These areas showed some mild diffusion restriction. The altered signal extended into the midbrain on the left side and there was also some involvement of the cortex in the right parietal lobe. Normal flow was seen in the basilar artery. Differential diagnoses of bilateral ischaemia, and progressive multifocal leukoencephalopathy were suggested. Posterior reversible encephalopathy syndrome was less likely due to the restricted diffusion. In the following 36 h, Hb had improved to 88 g/L, WCC remained at 5.0 × 10 9/L but Platelets had dropped to 1 × 10 9/L. Twelve hours later, her Hb was 78 g/L and platelets remained at 2 × 10 9/L. The blood film showed a few left shifted neutrophils but with a lack of red cell fragments. During this period, the CRP rose from 22 mg/L to 132 mg/L. Reticulocyte count was 146. Bilirubin was normal. Direct antiglobulin test was negative. Lactate dehydrogenase sample unfortunately haemolysed. A Heparin-induced Thrombocytopenia Antibody assay was not done as the patient was not on anticoagulants on admission and had not been prior to admission.

Bone marrow biopsy or a therapeutic intravenous infusion of immunoglobulin was not indicated so instead she was transferred to a tertiary centre for urgent plasma exchange due to the strong suspicion of TTP. This suspicion was suggested by neurological symptoms, anaemia, unexplained thrombocytopenia. Her PLASMIC score was 6 (high-risk; however, please note that the INR component missing). Table 1 provides an overview of the relevant investigations for this patient.

Cerebrospinal fluid analysis showed negative viral polymerase chain reaction testing, white cell count 12, red cell count 14, no organisms seen on microscopy, protein 0.53, and cytology acellular.

Electroencephalogram suggested an encephalopathic pattern with anterior sub-cortical slowing present. ADAMTS13 was normal and vWF cleaving protease was 106. Reticulocyte count was 3.98% and Fibrinogen 2.12 g/L. CT Thorax, Abdomen and Pelvis showed no abnormality.

A diagnosis of Linezolid induced Leukoencephalopathy was made.

She was discharged 8 weeks following presentation; making a complete recovery by 4 months.

MRI Head repeated at 9 months showed gradually reducing signal intensity in abnormal areas described earlier consistent with leukoencephalopathy. In addition her platelet count improved to 219 × 10 9/L upon discharge.

Discussion

In our case Toxic leukoencephalopathy is suspected in a patient presenting with focal neurology and recent use of a culprit medication [1].

Toxic leukoencephalopathy is a clinico-radiological diagnosis characterized by cerebral white matter injury on MRI due to a toxin [2].

It has been suggested that the addition of the term “acute” to toxic encephalopathy is reserved for patients with diffusion restriction to improve awareness of the Diffusion weighted imaging (DWI) findings in the early phase of this reversible neurological syndrome [3].

Acute Toxic Leucoencephalopathy, (ATL) presents acutely and features range from cognitive impairment to severe neurologic dysfunction including visual impairment.

MRI imaging in the acute or subacute phase can show relatively symmetry and involve the periventricular white matter on DWI out of proportion to their appearance on FLAIR images.

It is important to distinguish ATL from a more common condition called Posterior Reversible Encephalopathy Syndrome (PRES). PRES typically affects the cortices and subcortical white matter on FLAIR sequence; the periventricular white matter immediately around the ventricles is typically spared. Restricted diffusion is rare in PRES [3]. The decreased water diffusion is characterised by marked hyperintensity on DWI and hypointensity on ADC maps. Conversely, in posterior leukoencephalopathy syndrome the regions of vasogenic oedema are visualised as a hypointense or isointense signals on DWI and as markedly increased signals on ADC maps compared with normal brain tissue. None of the imaging markers appears to correlate with clinical outcome [3].

Reversibility of this diffusion restriction on follow-up MRI studies of toxic leukoencephalopathy has been reported. Potential reversible causes of ATL include chemotherapy, immunosuppressants, antibiotics, environmental toxins and drug abuse.

Histopathology has noted both intramyelinic and oligodendroglial swelling. Although exact pathophysiology is unclear, evidence shows white matter damage may occur directly from toxic injury on the myelin sheath or indirectly from capillary endothelial injury, or both [2].

Several differentials can be considered for the acute thrombocytopenia. Pseudothrombocytopenia needs considering but can be excluded following repeat FBC and blood film [4]. Although Post Transfusion Purpura can occur following transfusion, this generally occurs after only after 5 days [4]. Though the history of neurology, anaemia and thrombocytopenia are worrying for TTP, the lack of fragments and a within range ADAMTS13 went against this. Another differential was catastrophic Antiphospholipid Syndrome (cAPS); however a negative antiphospholipid antibody screen ruled this out. Other causes of PRES were excluded. There was no evidence of renal failure. Known hypertension was being treated with ramipril and was labile during admission (peaking at 170 mmHg systolic but averaging around 130 mmHg). Other tests for inflammatory syndromes were negative. Therefore, although there have been cases of diffuse restriction in PRES [5], PRES was considered very unlikely.

Table 1. Showing a summary of relevant investigations.

Investigation	Result
CT scan head	No mass, bleed, major territory infarct or extra-axial collection. No loss of grey-white matter differentiation. No vessel hyperdensity. Age-related cerebral atrophy noted. Peri-ventricular low attenuation in keeping with small vessel disease also present. No skull lesion or fracture.
MRI head with contrast	There is bilateral alteration of signal seen within the deep white matter of the posterior frontal and parietal lobes bilaterally. These areas show some mild restriction of diffusion. The altered signal extends into the midbrain on the left side. There is also involvement of the cortex in the right parietal lobe. These appearances are unusual and could represent bilateral ischaemia. However a normal flow void is seen in the basilar artery. There is a small established infarct in the left corona radiata. No other significant alteration of signal is seen in the brainstem, cerebellum or cerebral cortex.
Blood film	Red cell morphology: Anisocytosis White cell morphology: Toxic granulations in hypersegmented neutrophils Platelet morphology: Normal. True thrombocytopenia. Very few red cell fragments. No blast cells seen.

Other differentials included Immune Thrombocytopaenic Purpura (ITP), Haemolytic Uraemic Syndrome (HUS) and Disseminated Intravascular Coagulation (DIC). The history, normal renal function and clotting went against these differentials. The drop in platelet count was likely too acute for it to be drug related; the cause is unclear but could be immune, infection or drug related (the patient had received enoxaparin during the rehabilitative period).

The main differentials in our case were between TTP given the neurological sequelae and acute drop in haemoglobin and platelets, and Encephalitis. As mentioned earlier, the subsequent investigations, including blood film and CSF, meant both were considered to be less likely. The potential for rapid multiorgan dysfunction and availability of expertise and specialist treatments meant that tertiary transfer was important early in the patients' journey. Plasma Exchange was promptly started given the possibility of TTP or another immune mediated cause for the thrombocytopenia. Empirical treatments for Encephalitis were immediately commenced. IVIG treatment was felt to be unnecessary given this improvement and the possibility of TTP being unlikely. The importance of MDT collaboration was emphasised in our case, including early specialist referral and consideration of life threatening causes of thrombocytopenia as a priority.

Prior cases of toxic leukoencephalopathy have been described [4], including with Linezolid [5, 6]. The interval between Linezolid commencement and florid clinical features are however slightly longer in our case at 6 weeks compared to the 5 and 14 days respectively in the previous reported cases; and also include a more marked thrombocytopania and absence of leukopenia.

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Conflict of interest

The authors can confirm there are no conflicts of interest.

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Ethical approval

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Consent

Patient consent has been obtained.

Guarantor

Dr. Saad Ahmed is the guarantor for this report.

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