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Case Report

# Occurrence of Protein S Deficiency - Related Multisystem Thromboembolism in a Patient with Myelodysplastic Syndrome after Allogeneic Hematopoietic Stem cell Transplantation

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## ABSTRACT

**Introduction:** Haemostatic derangements in the post-transplant period are characterized by decreased levels of factor VII, factor X, protein C, antithrombin III, and plasminogen and increased levels of fibrinogen, von Willebrand factor, plasminogen activator inhibitor, and tissue plasminogen activator, predisposing recipients to both thrombotic and haemorrhagic complications. No changes in protein S level were seen. However, a prospective study by Abdelkefi, showed a 1.7% prevalence of asymptomatic protein S deficiency in the post-transplant setting. to date, no report of protein S deficiency – related complications post-transplant was published. Herein we present a patient with myelodysplastic syndrome who underwent hematopoietic stem cell transplant (HSCT) complicated by an array of complications brought about by protein S deficiency.

**Keywords:** Anti thrombin, Myelodysplastic syndrome, Hematopoietic stem cell transplant, Haemorrhage.

## CASE REPORT

A 54-year-old female from Malaysia with myelodysplastic syndrome underwent matched sibling donor HSCT with reduced intensity conditioning (RIC) using fludarabine 30mg/m$^2$/day from days -7 to -3, busulfan 3.2mg/kg from days -6 to -5, and cyclophosphamide 60 mg/kg/day on day -1. Cyclosporine and mycophenolate mofetil were given for graft versus host disease (GvHD) prophylaxis. Neutrophil engraftment was noted on day +11, however, platelet counts remained less than 50,000/uL.

The unusual complications that developed during the post – transplant period affecting the liver, brain, kidneys and lungs may be thromboembolic events as described below.

On day +9, the patient developed hepatic sinusoidal obstruction syndrome characterized by generalized jaundice, direct right upper quadrant tenderness, bipedal edema and weight gain with direct hyperbilirubinemia and hepatitis. Further tests showed normal prothrombin (PT) and activated partial thromboplastin time (aPTT) and elevated D-dimer.

On day +24, the patient had changes in sensorium accompanied by acute – onset headache followed by absence seizures. Cranial magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) showed increased T2-weighted signal in the bilateral amygdala and hippocampus and left basal ganglia but no vessel obstruction Figure 1A.

On day +44, acute kidney injury and ensuing pulmonary edema requiring ventilatory support developed. Hemodialysis was done as serum creatinine level increased to 2.9 mg/dL and estimated glomerular filtration rate dropped to 17.97 mL/min. Despite diagnostic measures, the etiology of kidney failure remained elusive.

Despite persistence of tachypnea by day +59, presence acute respiratory distress syndrome was unlikely since oxygen saturation was maintained with minimal supplementation. A chest computed tomography scan showed diffuse alveolar involvement. Figure 2A, 2B Bronchoscopy with bronchoalveolar lavage culture and quantitative viral studies ruled out possible infectious etiologies. Serial CXR revealed persistent bilateral pulmonary alveolar patterns or pneumonic infiltrates Figure 3A, 3B.

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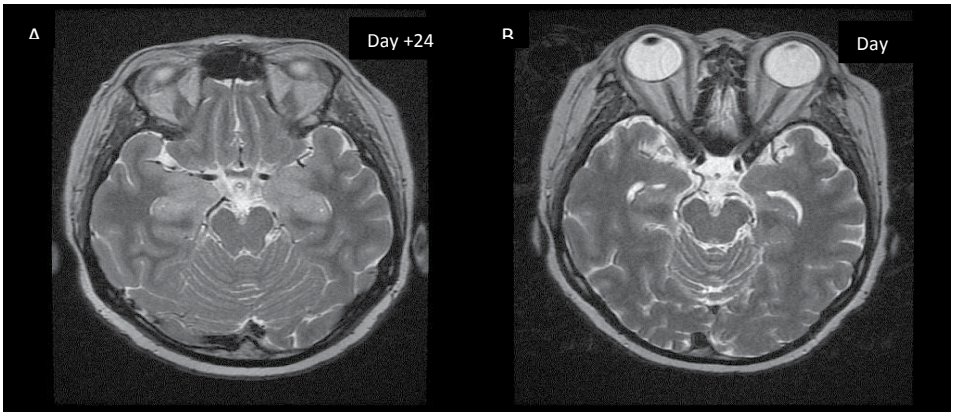


**Figure 1.** Cranial MRI showing increased T2-weighted signals in bilateral amygdala, hippocampus and left basal ganglia (A) and resolution after anticoagulation (B).

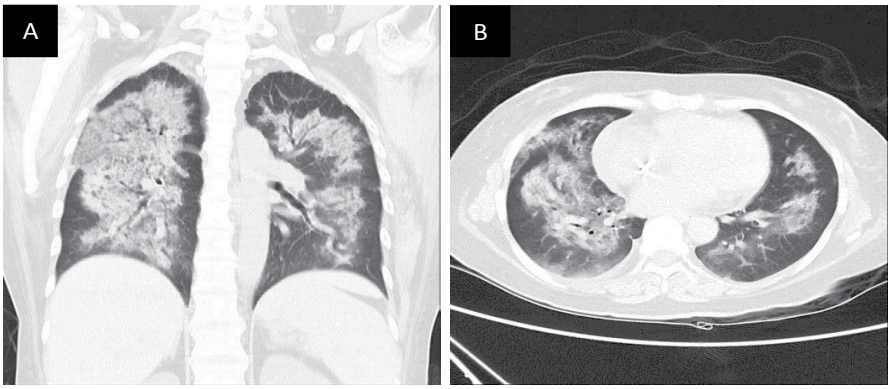


**Figure 2.** Coronal (A) and axial (B) views of chest CT scan showing diffuse alveolar involvement.

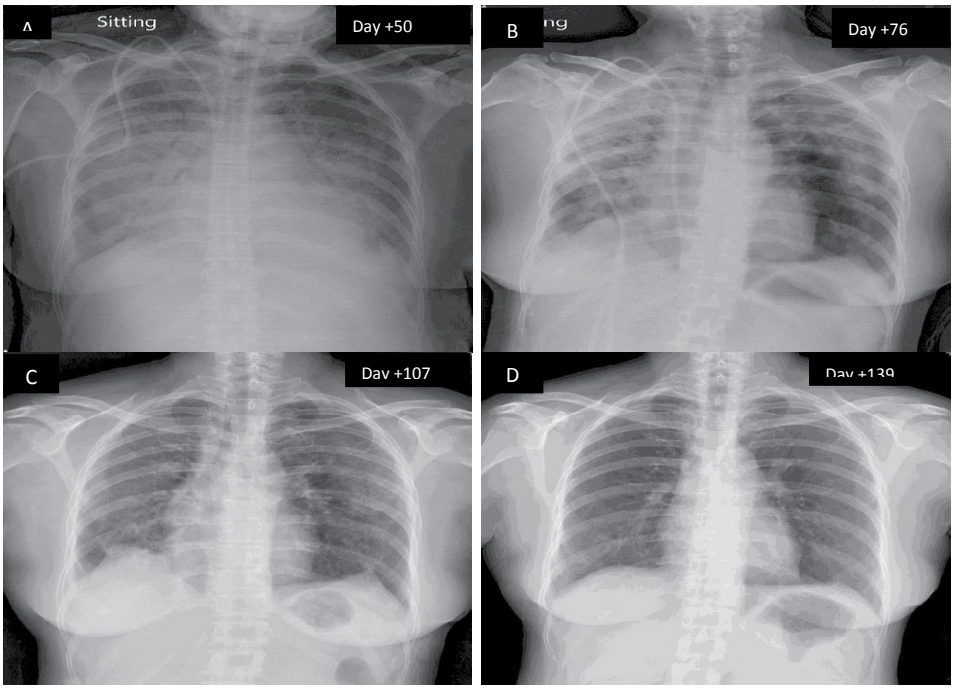


**Figure 3.** Serial chest radiographs showing progression of diffuse pulmonary infiltrates on both lung fields (A, B) and a chest radiograph showing complete resolution of infiltrates after 7 weeks of anticoagulation (C, D).

The unusual multisystem involvement, persistent elevation of D-dimer levels, serial PT, aPTT and fibrinogen monitoring that are within normal limits ruled out disseminated intravascular coagulation and raised the possibility of systemic thromboembolic events. A hemostatic system evaluation was performed on day +65, revealing a mildly elevated protein C (156.2%; normal value: 70 – 140%) and significantly decreased protein S levels (44%; normal value: 60 – 130%), hence the diagnosis of protein S deficiency. Anticoagulation was started on day +83 with subsequent dramatic clinical response, complete resolution of pulmonary infiltrates Figure 3C, 3D, normalization of D – dimer and recovery of platelet counts Figure 4. A follow – up protein S determination on day +108 showed decreased level at 53.8%. She was discharged asymptomatic on day +112 with out-patient follow-up.

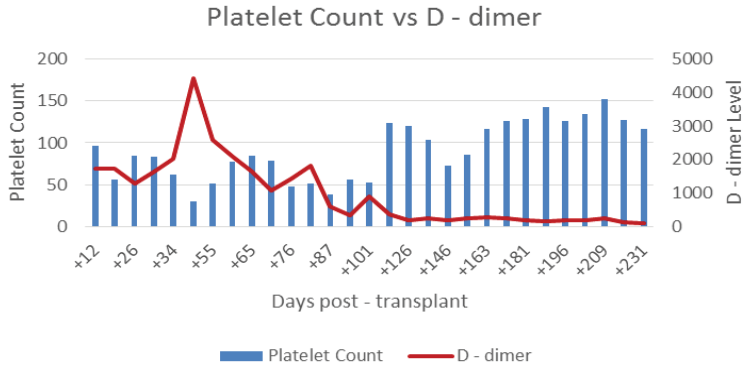


**Figure 4:** Improving platelet count with decreasing D-dimer levels after anticoagulation.

**Table 1:** Characteristics of patients who developed cerebral venous sinus thrombosis after hematopoietic stem cell transplant.

| Author | Age/Sex | Diagnosis | Type of Transplant | Presentation | Location | Presence of thrombophilia | Outcome after anticoagulation |
|---|---|---|---|---|---|---|---|
| **Fernandez (10)** | 61/F | MM | Autologous | Acute encephalopathy | Dural sinus thrombosis | none | Improvement of symptoms |
| **Motohashi (11)** | 42/F | AML | MUD Allogeneic | Headache, vomiting | Straight, transverse and sigmoid sinus | none | Resolution of symptoms |
| **Harvey (12)** | 15/M | Ph+ ALL | MSD Allogeneic | seizure | Transverse and sigmoid sinuses | none | Improvement of symptoms |
| | 13/M | ALL | MUD | headache | Sigmoid sinus | none | Improvement of symptoms; died of relapse |
| | 21/F | ALL | MSD | seizure | Cortical veins | none | Improvement of symptoms |
| **Bertz (13)** | 42/F | CML | MUD | Headache and seizure | Sagittal sinus | none | Improvement of symptoms |
| | 19/F | CML | MUD | Headache and seizure | Sigmoid | none | Improvement of symptoms |
| | 25/F | SAA | MUD | seizure | Transverse and sigmoid | Factor V Leiden Mutation | Improvement of symptoms |

MM – Multiple myeloma, ALL – Acute lymphoblastic leukemia, Ph+ - Philadelphia chromosome positive, AML – acute myeloid leukemia, CML – chronic myeloid leukemia, SAA – severe aplastic anemia, MUD – matched unrelated donor, MSD – matched sibling donor

## DISCUSSION

Protein S (PS) is a vitamin – K dependent plasma glycoprotein that functions as a co-factor of Protein C in the inactivation of FVa and FVIIIa. Only 40% of protein S has co-factor activity, while the remaining 60% is bound to C4b – binding protein. Protein S deficiency is a rare disorder, with an incidence of 0.16 – 0.21% in the general population [1-3]. Protein C and protein S deficiencies are most common among Asian population hence, it was considered in the initial work up for the patient. Factor V Leiden deficiency is more commonly recognized in Caucasians and laboratory testing was not available in our setting. This epidemiologic data was noted in a review by Kang – Ling et al stating that the incidence of protein C and S deficiencies were similar in Asians living in Asia and Asians living in western countries [4]. Deficiency can either be hereditary caused by PROS1 gene mutation, or acquired in several conditions like malignancies, use of oral contraceptive pills, nephrotic syndrome, pregnancy and vitamin K antagonist therapy. Deficient individuals typically present with unprovoked deep vein thrombosis, pulmonary embolism or both, and usually manifests around the fifth decade of life [3,4]. In the post-transplant setting, PS level was either normal or high [5].

Sinusoidal obstruction syndrome (SOS) is a serious complication of HSCT manifested as fluid retention, hepatomegaly and hyperbilirubinemia. Risk factors for developing SOS include pre-existing hepatic disease (e.g. viral hepatitis, iron overload), busulfan in combination with cyclophosphamide and allogeneic transplantation. The risk is downplayed by using RIC regimen. In a study from the Dana Farber Cancer Institute, there was a higher cumulative incidence of SOS in the myeloablative conditioning (MAC) at 9.6% vs RIC cohort at 1.6% ($p<0.0001$). Likewise, the median onset of SOS in the MAC cohort was 19 days compared to the RIC cohort of 26 days. The use of busulfan is another risk factor, however, in the same study, the risk of developing SOS after RIC is mitigated after a lower busulfan dosing [6,7]. Studies have also implicated protein C deficiency in the development of SOS [8,9]. The patient's SOS manifested at day +9, about a week earlier than expected despite the use of RIC conditioning with low dose busulfan and an elevated protein C level.

The neurologic complications immediately post-transplant are mainly infectious, drug-related or haemorrhagic in nature. Cerebral venous sinus thrombosis (CVST) is a rare condition accounting for <1% of all strokes in this time frame and is associated with multiple risk factors categorized as inherited such as thrombophilias or acquired as in trauma, surgery, malignancy, pregnancy, oral contraceptive pill use and infections. The pathophysiology is characteristically linked to the Virchow's triad of hypercoagulability, vessel wall injury and stasis of blood and

symptoms may vary from signs of increased intracranial pressure to manifestations of focal brain injury [10]. To date, only 8 such post-HSCT patients have been reported since the 1990's, and all of whom had no history of thrombophilia except for one that showed Factor V Leiden mutation Table 1. In these cases, headache, seizures and encephalopathy were the presenting symptoms [10-13]. Similarly, our patient presented with changes in sensorium, confusion, headache and seizures 24 days after HSCT. The MRI showed hyperintense T2 lesions in the hippocampus, amygdala and basal ganglia which may be due to infection, hypoxia and thrombosis in smaller vessels that cannot be totally ruled. These lesions and the symptoms had almost complete resolution after treatment with anticoagulation. Cyclosporine and tacrolimus were given for GvHD prophylaxis, the most common neurologic side effects of both drugs would be tremors and paresthesias, both are absent in our patient. The cyclosporine and tacrolimus levels were 95 – 115.3 ng/ml and 1.8 – 15 ng/ml respectively, levels that are within the desired limits. Posterior leukoencephalopathy syndrome associated with confusion, cortical blindness, seizures and visual hallucination may also be drug-induced but MRI findings usually shows multiple lesions in the white matter, particularly with occipital lobe with cortical involvement, lesions that are not present in our patient [14]. Cases of CVST associated with PS deficiency have been reported and were related to pregnancy [15], varicella infection [16] and tuberous sclerosis [17] but none was reported in relation to HSCT. Anticoagulation with enoxaparin was initiated following the diagnosis of Protein S deficiency with subsequent improvement in the patient's mental status and cognitive functions.

The etiology of acute kidney injury (AKI) following allogeneic HSCT is multifactorial and generally secondary to septicemia, SOS, thrombotic microangiopathy due to calcineurin inhibitors, GVHD, viral mediated, complement dysregulation, and total body irradiation. In a study of 186 subjects who underwent RIC, 44% developed AKI with a mean of 28 days. Identified risk factors were melphalan – based conditioning, unrelated donor and tacrolimus concentration [18, 19]. The renal complication of our patient manifested around day +44, long after the resolution of hepatic SOS. Lactate dehydrogenase determinations were normal, decreasing the likelihood of thrombotic microangiopathy and apart from acute skin GVHD controlled by steroids, no other risk factors for the development of AKI are present in our patient.

Pulmonary complications presented around day +44 as pulmonary edema and later at day +59 as infiltrates. Pulmonary complications post – HSCT may be related to infectious and non-infectious causes. In the absence of documented infection as in the case of our patient, differential diagnoses are narrowed to non-infectious causes such as diffuse alveolar hemorrhage (DAH) and idiopathic pneumonia syndrome (IPS). Diffuse alveolar hemorrhage is characterized bilateral lung infiltrates, progressively bloody return on BAL and >20% hemosiderin-laden macrophages in alveolar fluid. Widespread alveolar injury in IPS occurs in the absence of circulatory overload, cardiac and renal dysfunction and infections. Both DAH and IPN presents with dyspnea, non-productive cough, fever, and diffuse pulmonary infiltrates observed within the first month post-HSCT and differentiated by bronchoalveolar lavage (BAL) and pulmonary function testing (PFT) [20,21]. Risk factors present in our patient include age >40 years, allogeneic transplant and presence of GvHD. The initial symptoms seen in the patient resulted from pulmonary oedema precipitated by acute kidney injury where the symptoms gradually improved with diuresis and haemodialysis. The subsequent pulmonary findings at day +59 was attributed to diffuse alveolar haemorrhage as documented by bronchoscopy. No gross lesions were seen but the possibility of thrombosis cannot be entirely ruled out. Serial chest X-ray showed complete resolution of lung findings after initiation of anticoagulation Figure 3C, 3D.

In this multi – organ involvement, thrombotic microangiopathy was ruled out since the peripheral smear did not show presence of schistocytes and fragmented red blood cells. Serial monitoring of prothrombin and partial thromboplastic time

## CONCLUSION

Thrombosis secondary to protein S deficiency is an uncommon complication of HSCT. Its occurrence in the setting of reduced – intensity conditioning warrants a good index of suspicion and further evaluation of the haemostatic system especially in cases of multi-organ involvement. Diagnosis is confirmed by serial determination of protein S level and managed by initiation of anticoagulation.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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