Complications of Coagulopathy and Thrombosis secondary to Mucopolysaccharidosis type I at Autopsy

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Introduction

We present the findings of an autopsy case on an 18-month year old male of Caucasian descent with Mucopolysaccharidosis type I (MPS I). The decedent had undergone stem cell transplantation approximately one year prior, and was on immunosuppressive medications. He had a reported history of 1 day of vomiting and diarrhea prior to death. In addition to findings consistent with MPS I, autopsy revealed a saddle pulmonary embolism and features of dehydration.

Background

Mucopolysaccharidosis type I (MPS I) is an AR disease caused by mutations in IDUA gene, which encodes for the lysosomal enzyme alpha-L-iduronidase. The mutation leads to accumulation of the GAGs dermatan sulfate and heparan sulfate, which is responsible for the progressive multisystem dysfunction.

Affected patients typically have a phenotype consistent with either severe or attenuated MPS I, a distinction that influences therapeutic options. For cases of the severe phenotype of MPS I (about 54% of cases), infants appear normal at birth prior to the early manifestation which are non-specific (e.g., umbilical/inguinal hernia, URI's before age 1 year). Coarsening of the facial features may not be present until after the age of one year. Thoracolumbar kyphosis (Gibbus deformity) of the lower spine is often noted within the first year, and progressive skeletal dysplasia (dysostosis multiplex) and arthropathy of bones and joints respectively are usually observed. Cardiorespiratory involvement, hearing loss, and corneal clouding can be present from 6 to 12 months[1-2]. Without treatment, death (usually from cardiorespiratory failure) usually occurs within the first decade of life[1-2].

Case

The decedent was born at 39 weeks and newborn screen revealed no identifiable alpha-L-iduronidase enzyme (IDUA). Subsequent testing showed an elevated heparan sulfate and homozygous mutation in the IDUA gene c.1205G>A p.W402X, a common variant associated with the early-onset phenotype of MPSI (aka Hurler's syndrome).[1-2]

Coarse facial features (e.g. puffy cheeks, full lips, mild prognathism, and high-arched eyebrows), visceromegaly and multiplex dysostosis was present. ECG revealed prolonged QTc and left ventricular hypertrophy. Baseline echocardiogram revealed mildly thickened aortic valve leaflets without stenosis or regurgitation.

Treatment was initiated with enzyme replacement therapy and hematopoietic stem cell transplantation (HSCT) at 7 weeks & 7 months of life. HSCT achieved 30-day chimerism at 100% donor through all lineages.

His course was complicated by SARS-CoV-2, HHV6 PCR positivity, intermittent neutropenia, hypogammaglobinemia secondary to rituximab, hypertension, a history of skin abscess secondary to MRSA, and a fungal rash on the elbows and knees. Additionally, labs revealed fluctuating thrombocythemia.

The decedent had been evaluated two days prior to death and was doing well. The following day he developed a gastrointestinal illness. Autopsy revealed a dehydrated appearing child with saddle pulmonary embolism extending into segmental arteries bilaterally, loose yellow stool and bowel edema. No definitive infectious organisms or evidence of graft versus host was identified. Sampled bone marrow was unremarkable. No vitreous for electrolyte studies was able to be obtained secondary to desiccation.

Discussion

HSCT and its accompanying conditioning regimen has been associated with coagulopathy, albeit the potential contributory etiologies are numerous (infections, endothelial injury, vasculitis and GVHD to name a few). The decedent had fluctuating thrombocythemia (up to 762 k/mcl) of uncertain origin, and a clinical history of illness. As no evidence of GVHD or vasculopathy was present, underlying thrombocythemia with superimposed infection leading to vomiting, diarrhea and ultimately dehydration seem the most likely predisposing factors for pulmonary embolism. Dehydration can cause the blood vessels to narrow and blood to thicken which raises the risk of blood clotting.

Images

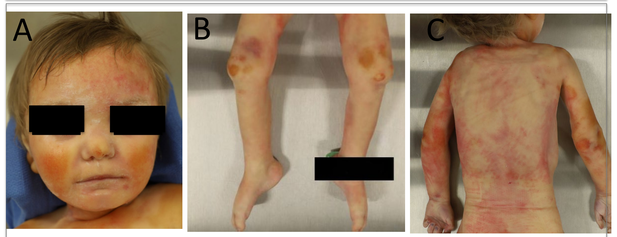

Image A. Coarse facial features characteristic of the severe subtype of MPS I (e.g flat nasal bridge, rounded cheeks, frontal bossing, midface retrusion)

Image B. Musculoskeletal defects of MPS 1 (e.g. contractures, valgus deformities of long bones & knees)

Image C. Thoracolumbar kyphosis (Gibbus deformity) of the spine

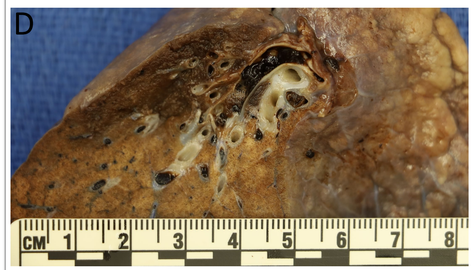

Image D. Pulmonary embolus with extension to segmental arteries

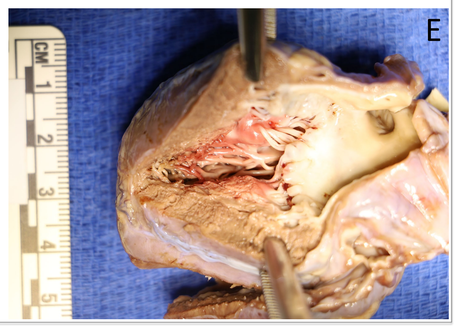

Image E. Redundancy and nodular myxoid changes in the mitral valve

Conclusions

Although stem cell transplants in MPS I patients have been proven to be effective, studies have demonstrated that pulmonary and infection-related deaths are often reported within the first post-transplant year. These incidences of mortality are commonly attributed to post-transplant factors such as GVHD, conditioning toxicity, and impaired immunity[4]. However, the differential of etiologies that may cause patients to be more susceptible to coagulopathy should also be considered. Literature and chart review revealed no identifiable cause for thrombocythemia in this patient, nor any such reported cases. Dehydration can cause the blood vessels to narrow and blood to thicken, raising the risk of blood clotting, which is suspected as a contributing factor in the development of the PE for this patient. We share this case to highlight the importance of monitoring and mitigating the modifiable risk factors for pulmonary thromboembolism in conjunction with a through autopsy evaluation to determine if transplant-related mortality can be excluded postmortem.

References & Acknowledgements

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