Unexpected coronary artery findings in mucopolysaccharidosis. Report of four cases and literature review

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Introduction: The mucopolysaccharidosis syndromes are a group of lethal inherited disorders affecting multiple organ systems by the progressive deposition of glycosaminoglycan. Advances in treatment such as enzyme replacement and hematopoietic stem cell transplantation have significantly improved the outcome of these disorders. An in-depth understanding of the pathophysiology of heart disease in these disorders is essential since death from cardiac causes continues to be common. Epicardial coronary artery luminal narrowing from myointimal proliferation and glycosaminoglycan deposition is well described in severe mucopolysaccharidosis type I [Hurler syndrome, mucopolysaccharide IH] but poorly understood in other “non-Hurler” phenotypes of these disorders. Given the rarity of these conditions, autopsy specimens are uncommon.

Methods: Tissue from epicardial coronary arteries from autopsies of four patients with non-Hurler mucopolysaccharidosis (attenuated type I, type II A, type II C, and type VI) who had died after hematopoietic cell transplantation (within 1 month in three cases; after 5 years in the fourth) was examined by light microscopy.

Results: Unexpectedly, near-normal coronary arteries were observed in the patient with attenuated mucopolysaccharidosis type I, while the coronaries from patients with type II A, II C, and VI demonstrated classic histologic features of glycosaminoglycan deposition. The most severe findings were found in the MPS II C patient who had 5 years of full donor engraftment after transplantation.

Conclusions: Our current understanding of the cardiac manifestations of the mucopolysaccharidoses fails to explain why near-normal coronary arteries may be observed when abnormalities would be most likely to be expected and, conversely, why significant histopathology is present when it would be least expected. Identification of downstream effects of glycosaminoglycan deposition may identify other metabolites or metabolic pathways that are important in the clinicopathologic manifestations of these diseases.

Summary: The mucopolysaccharidosis diseases are a group of inherited disorders affecting multiple organ systems by the progressive deposition of glycosaminoglycan. Severe coronary artery disease is well recognized in severe type I mucopolysaccharidosis (Hurler syndrome), but unexpected coronary artery disease occurs in other, “non-Hurler” mucopolysaccharidoses. Factors responsible for the development of coronary pathology in the mucopolysaccharidoses remain elusive.

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1. Introduction

The mucopolysaccharide (MPS) disorders are a group of inherited lysosomal storage diseases resulting from deficient enzymes responsible for the catabolism of glycosaminoglycan (GAG), complex heteropolysaccharides intrinsic to all mammalian tissues [1, 2]. Depending upon the missing enzyme, specific types of GAG accumulate (Table 1). Accumulation of GAG results in the clinical features of these disorders, including dystosis multiplex and coarsening of skin and facial features, as well as central nervous system (CNS), respiratory, and cardiac insufficiency [1]. The specific MPS types are defined by determination of the missing enzyme activity and urinary excretion of the corresponding GAG, with each type having clinical similarities to, and differences from, the others. Numerous mutations have been identified within each gene responsible for the specific type of MPS [3–10], and although some genotype–phenotype correlations are recognized, much remains unknown. Severe MPS I (Hurler syndrome) is the second most
commonly recognized MPS syndrome [5] and, if untreated, results in profound CNS, respiratory, and cardiac involvement from the relentless accumulation of GAG with death occurring within the first decade of life [1].

Cardiovascular involvement in Hurler syndrome includes deposition of GAG in the myocardium, cardiac valves, great vessels, and coronary arteries [11]. The myocardium is hypertrophied by the infiltration of GAG which may lead to systolic and diastolic dysfunction [12]. Cardiac valves (predominantly mitral and aortic) are thickened and become significantly regurgitant or stenotic. Both dilation and coarctation of the aorta have been reported [13,14]. GAG deposition within the epicardial coronary arteries initiates myointimal proliferation that, in turn, produces severe and diffuse narrowing of these vessels (Fig. 1) [11,15].

Cardiac pathologic findings vary depending upon MPS type, which, in part, is thought to be dependent upon the type of GAG stored [1]. For example, cardiac valve involvement is believed to be more severe in MPS I, II, and VI, types that include the deposition of dermatan sulfate [16–19]. While the coronary arteries are severely affected in Hurler syndrome [11], coronary involvement in “non-Hurler” MPS is poorly understood, with both presence and absence of coronary disease alternatively reported in all types of non-Hurler MPS, including attenuated MPS I (Table 2) [14,15,18,20–48].

Over the past 30 years, the previously dismal natural history of the MPS syndromes has been significantly improved by hematopoietic cell transplantation (HCT) for Hurler syndrome [49–52] and the availability of recombinant enzyme replacement therapy (ERT) for attenuated MPS I, MPS II, and MPS VI [53–55]. The cardiac effects of HCT and ERT include preservation of ventricular function and resolution of ventricular hypertrophy, but established cardiac valve pathology appears unaffected by either therapy [56–59]. Arrest or regression of coronary pathology has been shown in a single patient with MPS IH 14 years after HCT [27], but the effects of ERT on established MPS coronary disease appears variable and may, as has been found for the valves, depend upon the severity of disease present when ERT is begun [21,22,28,33].

Determining the risk of coronary artery disease in non-Hurler MPS is currently an important but overlooked task, both because coronary artery disease can be a cause of morbidity and mortality and because the presence of significant coronary narrowing is an important risk factor for individuals undergoing invasive procedures [60]. Individuals with MPS commonly require surgical correction of skeletal manifestations of the disease that do not respond to either HCT or ERT, including orthopedic surgery for hip and knee dysplasia [61,62] and emergency cervical cord decompression from GAG deposition within the dura in association with atlanto-occipital instability [63]. To increase our understanding, we present coronary artery histology from four “non-Hurler” MPS patients who demonstrated unexpected coronary artery pathology and a review of the known coronary artery findings, either by angiography or histology, in cases where the MPS diagnosis has been affirmed by urinary GAG and/or assay of corresponding enzymatic activity.

Table 1

<table>
<thead>
<tr>
<th>Mucopolysaccharidoses</th>
<th>Enzyme deficiency</th>
<th>Stored GAGs</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS I severe, attenuated</td>
<td>α-L-iduronidase</td>
<td>Heparan sulfate, dermatan sulfate</td>
</tr>
<tr>
<td>MPS II severe, attenuated</td>
<td>Iduronate 2-sulfatase</td>
<td>Heparan sulfate, dermatan sulfate</td>
</tr>
<tr>
<td>MPS III A</td>
<td>Heparan sulfate sulfatase</td>
<td>Heparan sulfate</td>
</tr>
<tr>
<td>MPS III B</td>
<td>N-acetyl-α-L-glucosaminidase</td>
<td>Keratan sulfate, chondroitin-6-sulfate</td>
</tr>
<tr>
<td>MPS III C</td>
<td>α-glucosaminidase</td>
<td>Chondroitin-4-sulfate, keratan sulfate, dermatan sulfate, heparan sulfate</td>
</tr>
<tr>
<td>MPS III D</td>
<td>N-acetylglucosamine-6-sulfatase</td>
<td>Keratan sulfate, chondroitin-6-sulfate</td>
</tr>
<tr>
<td>MPS IV A</td>
<td>Galactosamine-6-sulfatase</td>
<td>Keratan sulfate, chondroitin-6-sulfate</td>
</tr>
<tr>
<td>MPS IV B</td>
<td>β-galactosidase</td>
<td>Chondroitin-4-sulfate, dermatan sulfate, keratan sulfate</td>
</tr>
<tr>
<td>MPS VI</td>
<td>Asylsulfatase B</td>
<td>Chondroitin-4-sulfate, dermatan sulfate</td>
</tr>
<tr>
<td>MPS VII</td>
<td>β-glucuronidase</td>
<td>Chondroitin-4-sulfate, dermatan sulfate</td>
</tr>
</tbody>
</table>

Fig. 1. (A–C) Intimal thickening (bars) is identified within the epicardial coronary arteries of patients with (A) MPS IIIA (thickness 80 μm) (Alcian blue, 40×), (B) MPS IIIC (thickness 597 μm) (ELVG, 10×), and (C) MPS VI (thickness 75 μm) (Alcian blue, 20×).
Table 2
Coronary artery involvement in the mucopolysaccharidoses — literature review

<table>
<thead>
<tr>
<th>Type MPS, untreated</th>
<th>Coronary artery involvement present (reference)</th>
<th>Normal coronary arteries (reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-10-month-old male with occlusion of left coronary artery by angiography 3 months of ERT [14]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-3.5-year-old male with intimal thickening after 1 year of ERT [15]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-9-year-old female [10]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-14-month-old male with myointimal proliferation [16]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-5-year-old male diffuse coronary narrowing at autopsy [8]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-5 patients, aged 6–16 years [3]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-Unknown age and sex [17]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-6-year-old male [18]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-8- and 9-month-old females [19]</td>
<td></td>
</tr>
<tr>
<td>I, attenuated</td>
<td>-20-year-old male with acute infarct of right papillary muscle after 2 years of ERT [21]</td>
<td>-52-year-old male angiography only [22]</td>
</tr>
<tr>
<td></td>
<td>-56-year-old male diffuse right coronary narrowing by angiography only [22]</td>
<td>-35-year-old female angiography only [25]</td>
</tr>
<tr>
<td></td>
<td>-20-year-old female stenosis of right coronary artery [23]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-15-year-old male with thickened coronaries and nests of Gargoyle cells [24]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-27-year-old male with apical aneurysm [27]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-30-year-old male with MPS II and SLE [28]</td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>-20-year-old male with thickened coronaries [29]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-11-year-old male: coronary arteries not specifically mentioned; foam cells present in intima and media of arterial walls [31]</td>
<td>-10-year-old male: coronary arteries not specifically mentioned; aorta and bigger arteries not involved [32]</td>
</tr>
<tr>
<td>IIIB</td>
<td>-9-year-old female with coronary thickening noted [33]</td>
<td>No known reports</td>
</tr>
<tr>
<td>IIV</td>
<td>-35-year-old female with large and medium-sized arteries with intimal thickening and vacuolated cells [34]</td>
<td>No known reports</td>
</tr>
<tr>
<td></td>
<td>-13-year-old male: coronary arteries not specifically but extensive vacuolar cytoplasmic storage in arteries [31]</td>
<td></td>
</tr>
<tr>
<td>IVD</td>
<td>-No known reports</td>
<td>No known reports</td>
</tr>
<tr>
<td>III, undefined</td>
<td>-8-year-old female with intimal thickening of coronary arteries [35]</td>
<td>No known reports</td>
</tr>
<tr>
<td>IVB</td>
<td>-No known reports</td>
<td>No known reports</td>
</tr>
<tr>
<td>VI</td>
<td>-27-year-old male [38]</td>
<td>No known reports</td>
</tr>
<tr>
<td></td>
<td>-22-year-old male with LV apical aneurysm and small coronary vessel disease [39]</td>
<td></td>
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<tr>
<td></td>
<td>-43-year-old male angiography showed mild nonobstructive atheromatous disease [40]</td>
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<td></td>
<td>-38-year-old male with severe coronary sclerosis with complete LAD occlusion [40]</td>
<td></td>
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<tr>
<td></td>
<td>-38-year-old male narrowed coronary ostia but otherwise normal coronary arteries [40]</td>
<td></td>
</tr>
<tr>
<td>MPS VII</td>
<td>-19-year-old male with eccentric fibrous plaque and 95% narrowing of LAD [41]</td>
<td>No known reports</td>
</tr>
</tbody>
</table>

Table 3
Summary of MPS autopsy cases in current study

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Type MPS</th>
<th>BMT</th>
<th>Clinical cardiac disease</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>M</td>
<td>Attenuated MPS I</td>
<td>Death 4 weeks after BMT</td>
<td>Yes</td>
<td>Minimal&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>F</td>
<td>MPS IIIA</td>
<td>Death 16 days after BMT</td>
<td>No</td>
<td>Moderate&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>M</td>
<td>MPS IIIC</td>
<td>Death 5 years after BMT; fully engrafted BMT #1; death 2 weeks after BMT #2</td>
<td>Yes</td>
<td>Severe&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>M</td>
<td>MPS VI</td>
<td>Failed engraftment BMT #1; death 2 weeks after BMT #2</td>
<td>No</td>
<td>Moderate&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> See text for detailed description.

ages 6 and 15 years, respectively, and subsequently developed incomplete right bundle branch block and first-degree heart block with episodes of atrial flutter and atrial fibrillation. An echocardiogram prior to HCT demonstrated moderate to severe left ventricular dysfunction with an ejection fraction of 30%, moderate/severe tricuspid regurgitation with right atrial enlargement, trivial prosthetic aortic insufficiency, and mild prosthetic mitral regurgitation. He underwent HCT, but developed massive intracerebral hemorrhage 4 weeks later and died.

At autopsy, moderate cardiomegaly, functional prosthetic mitral and aortic valves, moderate right atrial dilation, and biventricular dilation and hypertrophy were found. The coronary artery walls showed minimal to mild fibrous thickening on gross inspection.

3.2. Case 2

A 2-year-old female was evaluated for mild developmental delay at age 1 year and was diagnosed with MPS IIIC with documented urinary excretion of heparan sulfate and decreased fibroblast heparan sulfamidase levels. She underwent bone marrow transplantation at age 2 years that was complicated by Klebsiella sepsis, respiratory distress syndrome, and hepatic and renal failure. She also developed grade III graft-versus-host disease. She suffered an intracranial hemorrhage and died 16 days after receiving her graft.

At autopsy, the heart weight and left ventricular wall thickness were greater than normal. The coronary arteries had normal caliber and branching on gross inspection.

3.3. Case 3

A 12-year-old male was diagnosed with MPS IIIC at age 7 by deficiency of acetyl CoA:α-glucosaminide acetyltransferase. He underwent HCT, and full donor engraftment was documented on multiple occasions, including 3 months before death.
Prior to HCT, he had undergone protocol-driven cardiac catheterization that was remarkable for abnormal response of left ventricular end-diastolic pressure with an increase from 12 to 19 mmHg after a 5-ml/kg normal saline bolus. By angiography, the left ventricle was described as moderately enlarged with generalized diffuse mild hypokinesia. Selective coronary angiography showed slow flow through the left coronary artery with paucity of distal branches, although the right coronary artery was normal.

Three years after successful HCT, he was hospitalized for fever and respiratory distress and developed complete heart block requiring emergency transvenous pacing for 4 days. When AV conduction returned, he underwent an intravascular electrophysiological study that showed normal AV conduction to a cycle length of 220 ms. Autonomic blockade did not change his AV or sinus node function, and no pacemaker was placed. Some 5 years after HCT, he was admitted for diarrhea, fever, and confusion. He progressed to develop severe gastrointestinal bleeding and multisystem organ failure and died.

At autopsy, inspection of the coronary arteries showed mild thickening with mild luminal narrowing proximally greater than distally. The right coronary ostium was mildly slit-like, while the left ostium was normal.

4. Histopathological findings

Features of MPS-like coronary disease were found within the large epicardial coronary arteries in all four of these patients. The coronary intima was thickened in the patients with MPS IIIA (80 µm), MPS IIIC (597 µm), and MPS VI (75 µm) (Fig. 1 A–C, black bars), and the presence of typical plump clear cells was seen in the intima, media, and adventitia of each case (Fig. 2 A–C, white arrows). Surprisingly, the coronary intimal layer was of normal thickness in the 19-year-old with attenuated MPS I (Fig. 3, black arrow). In this patient, the presence of typical plump clear cells within the adventitia was the only evidence suggestive of MPS (Fig. 3, white arrow). Disruption and fragmentation of the elastic fibers were identified in the coronary arteries from cases of MPS IIIA (Fig. 4A) and MPS IIIC (Fig. 4B); the elastic lamina appeared intact in cases of MPS I (not shown) and MPS VI (Fig. 4C).

5. Discussion

Autopsy cases of MPS are exceedingly rare as evidenced by the availability of only four non-Hurler MPS cases identified over the past 30 years at our institution, a center with a long-standing focus in the treatment of MPS. Remarkably, unexpected histopathological findings were present in each of the four cases. In keeping with the unpredictable nature of coronary artery pathology in non-Hurler MPS, there appeared to be minimal histopathological findings in the patient with attenuated MPS I when changes would be most likely expected. Conversely, moderate to severe deposition of GAG and the robust presence of clear cells occurred in MPS IIIA, MPS IIIC, and MPS VI, diseases in which they would be least anticipated.

The absence of significant coronary involvement in our case of attenuated MPS I is unusual and, until now, has only been documented by others angiographically (Table 2). Significant coronary involvement has been described by several authors: Wassman and colleagues were the first to report stenosis of the right coronary artery in a 20-year-old female with attenuated MPS I who had died suddenly [30]. Subsequently, diffuse coronary artery narrowing was also described in a 35-year-old male who probably had attenuated MPS I.
MPS I but had been identified as MPS V at the time [31]. Diffuse long segment narrowing of the right coronary artery was shown in a 56-year-old male by angiography [29]. Finally, two years of ERT did not appear to prevent death from presumed coronary artery involvement in a 20-year-old male who died with a recently infarcted right papillary muscle [28]. Our present case (case 1) is all the more remarkable because the coronary artery involvement appeared to bear no relationship to the cardiac valve pathology that had been severe enough to require replacement of both mitral and aortic valves.

The presence of myointimal proliferation and the presence of clear cells in our cases of MPS IIIA (case 2) and MPS IIIC (case 3) are also unexpected because, until recently, pathological findings in this type of MPS were thought to be limited to the CNS [18,64]. The coronary arteries have not specifically been described in most cases of MPS IIIA, although the aorta and “larger arteries” have been described in some cases as normal [39] or in others as abnormal [38]. In other reported cases of MPS IIIA, coronary artery status is not discussed [64,65]. In a case of MPS IIIC, the coronary arteries of a 39-year-old female showed sclerosis and thickening of the walls [41]. Coronary intimal thickening was reported at postmortem examination in an 8-year-old female with MPS III, but unfortunately, diagnosis was made only by urinary GAG identification, not by absence of functional enzyme, so the specific type of MPS III was not known [42].

Our two cases of MPS III are remarkable for several reasons: firstly, for MPS IIIA, this is the first histopathological demonstration of unambiguous coronary artery myointimal proliferation and observed at a very young (2 years) age. Secondly, in the case of MPS IIIC, the myointimal proliferation is severe and likely contributed to the patient’s ongoing cardiac dysfunction and unfavorable outcome after HCT. Persistent coronary artery involvement in this patient despite several years of complete donor engraftment after bone marrow transplantation is in stark contrast to the experience with MPS I [27]. Although heparan sulfate GAG has long been thought to be the only GAG accumulated in MPS III, it has recently been reported that there is a two- to fivefold increase in dermatan sulfate accumulation in MPS III cultured fibroblasts when compared to normal cells [66]. In these fibroblasts, heparan sulfate accumulation causes downstream inhibition of iduronidase 2-sulfatase, one of the lysosomal enzymes responsible for dermatan sulfate degradation. It has been postulated that there is sufficient heparan sulfate in vivo to produce similar results, thus perhaps explaining the presence of somatic involvement in MPS III. Accumulation of dermatan sulfate has previously been shown to prevent the assembly of tropoelastin into elastin [13], resulting in fragmentation of elastin fibers, as was also seen in both of our cases of MPS III (Fig. 4).

Finally, the occurrence of coronary artery involvement in MPS VI (case 4) has rarely been reported. Intimal thickening with the presence of foam cells was described at postmortem in a 27-year-old male with MPS VI (Maroteaux–Lamy) [45]; small vessel coronary disease was reported in a patient with MPS VI who developed a large left ventricular apical aneurysm, but the epicaldary coronary arteries were described as normal [46]. In the adult cases of MPS VI described by Wilson et al. [47], no histopathological images were presented, so it is unclear whether the coronary disease was consistent with MPS VI coronary disease or, given the age of the patients, atherosclerotic disease. Our case of MPS VI showed that intimal proliferation and the presence of clear cells within the intima, media, and adventitia had already occurred by 3 years of age. Remarkably, and inexplicably, the internal elastic lamina appeared intact and the elastic fibers appeared normal despite the fact that the GAG stored in MPS VI is dermatan sulfate (Fig. 4).

The micrographs presented in this study were obtained from the epicardial coronary arteries obtained at routine autopsy; tissue was not decalcified, and a detailed interrogation of each coronary artery was not performed. It has long been known, however, that MPS coronary disease is a diffuse process affecting the entirety of the epicardial coronary arteries in marked contrast to the more focal nature of atherosclerotic coronary disease [15]. As a result, sampling of any part of the epicardial coronary artery in MPS is likely representative of the entire epicardial coronary artery.

Although an increased risk of premature cardiovascular disease is a long-term effect of hematopoietic cell transplantation [67], the micrographs presented in this study demonstrate features typical of MPS coronary arteriopathy rather than the anticipated atherosclerotic disease seen after HCT. Additionally, the atherosclerotic disease seen after HCT is quite rare and usually occurs in adults and at a much later time (average of 9 years post-HCT in reference cited) than those of the current study.

In summary, although individuals with Hurler syndrome uniformly exhibit severe, progressive coronary artery occlusion, little is known about the incidence or severity of coronary artery involvement in other MPS conditions. The downstream effects of GAG accumulation in promoting myointimal proliferation remain largely unstudied. The cases presented here have shown that coronary involvement can occur in types of MPS where it is least expected and may be absent when it is most anticipated. Predicting the risk of coronary involvement in MPS conditions other than Hurler syndrome is clinically important but not currently possible based upon our present understanding of GAG pathobiology. Predicting clinical coronary obstruction will likely be dependent upon understanding the downstream pleiotropic effects of GAG accumulation on vascular biology and identifying common element(s) that may initiate the cascade of events that produces coronary disease regardless of the type of MPS disease.

References


