Complex Management of a Patient with Chiari Malformation, Ehlers-Danlos Syndrome, Postural Orthostatic Tachycardia Syndrome, and Mast Cell Activation Syndrome

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Abstract

Ehlers-Danlos Syndrome (EDS), Postural Orthostatic Tachycardia Syndrome (POTS), and Mast Cell Activation Syndrome (MCAS) have been reported to be a possible triad with hereditary alpha-tryptasemia a possible unifying pathophysiologic mechanism. Here, we report a patient with EDS, POTS, and MCAS who underwent surgery for Chiari malformation. The patient had consistently low serum tryptase levels, suggesting that hereditary alpha-tryptasemia was unlikely to be the common link between her syndromes. We describe challenges in her postoperative care due to many complications from her comorbid diseases and the need for better understanding the relationship between EDS, POTS, and MCAS.

Introduction

Ehlers-Danlos Syndrome (EDS) is a connective tissue disorder characterized by hyperextensibility of the skin, tissue fragility, and joint hypermobility [1]. Patients with EDS are at a higher risk of developing Chiari Malformation I (CM1), radiographically defined as herniation of the cerebellar tonsils by at least 3 mm to 5 mm below the level of the foramen magnum. CM1 patients suffer from a variety of symptoms, including sub occipital pressure headaches, ataxia, paresthesia, and cranial nerve deficits, and they typically undergo surgical decompression of the posterior fossa, with Occipitocervical Fusion (OCF) if Craniocervical Instability (CCI) is also present [2]. Patients with comorbid EDS are at higher risk for postoperative complications due to their poor wound healing and skin fragility [3]. In these high-risk patients, myofascial flap closure may be beneficial because usage of the paraspinous and trapezius muscles for flap creation can obliterate dead space and provide vascularized coverage of hardware and bone grafts [4,5].

EDS has also recently been described as part of a rare triad with Postural Orthostatic Tachycardia Syndrome (POTS) and Mast Cell Activation Syndrome (MCAS). POTS is defined by orthostatic intolerance and symptoms of dysautonomia, such as syncope and changes in heart rate [1]. MCAS, a subtype of Mast Cell Activation Disorder (MCAD), is characterized by increased number and/or activity of mast cells, which play a key role in homeostasis, immune surveillance, response to tissue injury, allergic reactions [6]. Patients with MCAS exhibit symptoms consistent with aberrant mast cell mediator release, such as flushing, pruritus, urticaria, and anaphylaxis [6]. Elevated basal serum tryptase levels have been associated with phenotypes common to the triad, but there is yet to be conclusive evidence linking these three chronic diseases and much is still unknown [1].

Here, we report a middle-aged woman with a history of EDS, POTS, and MCAS who underwent surgical management for her CM1 and CCI but had multiple postoperative complications. We describe challenges faced during management of these complications and the importance of recognizing the EDS-POTS-MCAS triad.

Case Presentation

Preoperative presentation

Ms. A, a 37-year-old woman with EDS, POTS status post pacemaker placement for bradycardia, and MCAS, presented to our office with years of daily sub-occipital headache, visual symptoms,
and diffuse paresthesias in the extremities, imbalance, tinnitus, and urinary disturbances. Her brain MRI showed a mild tonsillar ectopia 4 mm below the foramen magnum without a hydrocephalus or syrinx, consistent with CCI. She showed a positive response to 6 weeks of cervical collar trial, which reversibly improved her symptoms and increased our suspicion for underlying CCI. Thus, to address her CCI and CM1, posterior Fossa Decompression (PFD) and OCF were planned, and plastic surgery was involved for myofascial flap closure.

Of note, Ms. A had an extensive list of antibiotic and food allergies. Antibiotic allergies included cefazolin, cephalosporins, clindamycin, levofloxacin, penicillins, sulfamethoxazole-trimethoprim, vancomycin, and doxycycline. The patient had anaphylaxis reactions for all of the listed antibiotics, except for doxycycline. Food allergies included gluten meal, pistachio nut extract, strawberry, apple, corn, lactase, lactalbumin, peanut, potatoes, quinoa, raspberry, rice, soy, soybean oil, strawberry C (ascorbate), sugar-protein-starch, and wheat. Other allergies included adhesive tape, cat, gadolinium, diphenhydramine, Lac Bovis, latex, mold, ragweed, and silicone. Reactions to these allergens ranged from facial swelling, rashes, hives, and GI upset to anaphylaxis.

Postoperative complications and management after surgery of the craniovertebral junction

Thirteen days after her PFD with OCF and myofascial flap closure, Ms. A was readmitted due to a superficial Methicillin-Resistant Staphylococcus aureus (MRSA) infection of the surgical site without involvement of the hardware. She developed significant generalized pruritus after starting IV daptomycin, so she received premedication with IV Benadryl and PO prednisone. She underwent incision and drainage and subsequent surgical washout with JP drain placement.

Her postoperative hospital course was complicated by anaphylactic reactions to food, which required IM epinephrine, albuterol, and IV Benadryl. Tryptase levels were measured to be <2 ng/mL (upper limit of normal is 11.4 ng/mL) [7]. Ms. A, experienced recurrent episodes of anxiety and dyspnea without hemodynamic changes, and she did not tolerate a hypoallergenic nasogastric tube feed due to rash and itching. After discussion with her outpatient allergist, she was started on omalizumab with which she tolerated a regular diet. Ms. A was discharged with plan for follow-up and continuation of daptomycin on a Peripherally Inserted Central Catheter (PICC) line for a total of 2 weeks after washout.

Two months after her discharge, the patient had a recurrence of the MRSA infection, now with hardware involvement, so she had to undergo a deep wound surgical washout with myofascial flap closure. The patient tolerated the procedure well, and she was started on a 6-week course of IV daptomycin with Benadryl premedication.

Given the hardware involvement, after the 6-week antibiotic course, the patient required transition to chronic oral antibiotic suppressive therapy. However, given her extensive list of drug allergies, the patient had to undergo doxycycline desensitization with PO Benadryl premedication. The patient was then discharged with PO doxycycline for long-term suppression therapy. Due to adverse side effects (pruritus, nausea/vomiting, and cough) a low dosage of doxycycline (100 mg daily) was initially used. However, the MRSA infection broke through again on this regimen, so doxycycline dosage was increased to 200 mg daily. On this higher dosage, side effects were controlled with Benadryl, and the dosing regimen was changed from 100 mg BID to 50 mg QID.

Eight months after her initial surgery, after adequate fusion was verified by CT scan, hardware removal was warranted to decrease the need for chronic antibiotic suppression therapy. Preoperatively, the patient prophylactically took prednisone and Singular for her MCAS and any possible allergic reactions. Her postoperative course was uneventful and her neurologic symptoms resolved without the need of a cervical collar.

Discussion

There have been a few reports suggesting an association between MCAS, EDS, and POTS. In one pilot study, 66% of patients with previously diagnosed EDS and POTS reported symptoms concerning for MCAS [8]. A series of studies linked the triad with hereditary alpha-tryptasemia as a possible underlying condition [1].

Hereditary alpha-tryptasemia is an autosomal dominant condition caused by germline duplications or triplications in TPSAB1, the gene that encodes alpha-tryptase. This increased copy number of TPSAB1 leads to elevated levels of basal serum tryptase (>8 ng/mL), a protease released by activated mast cells. These germline mutations also present with other phenotypes, such as abnormal connective tissue (e.g. hypermobility type EDS), dysautonomia (e.g. POTS), and MCAS symptoms. This constellation of different phenotypes, elevated serum tryptase, and increased TPSAB1 copy number has been tentatively designated as hereditary alpha-tryptasemia syndrome [9]. Given such clinical patterns, it has been hypothesized that this syndrome could link the triad of EDS, POTS, and MCAS [1]. However, it is unclear what role elevated tryptase plays in this cluster, and further investigation is needed to determine whether there is truly a causal relationship between tryptasemia and the triad [1].

Interestingly, our patient consistently had low basal serum tryptase levels. Thus, despite having EDS, POTS, and MCAS, she had a low pre-test probability of hereditary alpha-tryptasemia and did not undergo tryptase genotyping. Contrary to the prior theory, tryptase did not appear to play a significant role in this case. Given the complex nature of each of the three diseases in the triad, there are likely multiple pathophysiologic variations.

Due to EDS, this patient was already at high baseline risk of postoperative complications and delayed wound healing. Additionally, due to Ms. A’s allergies to adhesives, the site of surgical incision was covered with Steri-Strips without any use of tissue glue, following the skin closure. Though there have not been any studies comparing tissue glue and Steri-Strips in this particular patient population, studies involving cleft palate repairs have shown that infection and revision rates were lower when tissue glue was used, compared to Steri-Strips alone [10].

When the patient was readmitted with the MRSA wound infection, her MCAS and extensive allergies to most antibiotics made treatment of her infection complex. Because of her recurrent anaphylactoid reactions and development of rashes, selection of medications and advancement of diet had to be done with care. For example, though vancomycin is traditionally the initial antibiotic choice for MRSA infections, daptomycin, an equally effective but more costly choice, had to be selected instead [11]. Furthermore, Ms. A had to be premedicated with Benadryl for her IV daptomycin, and she had to undergo doxycycline desensitization for her long-term oral antibiotic regimen.

Management of patients with EDS can be challenging because...
they often present with other comorbid diseases, such as CM1 [3]. In particular, EDS type III (hypermobility type) has been reported to be the most common disorder associated with POTS, although the mechanistic association between dysautonomia and joint hypermobility is not understood [12,13]. Because of their increased risk of wound healing problems, these EDS patients often require more careful postoperative monitoring for complications. As in our case, when surgical patients with a history of the EDS-POTS-MCAS triad present with postoperative complications, a multidisciplinary approach involving neurosurgeons, plastic surgeons, allergists, nutritionist, and infectious disease specialists is essential for addressing the unique needs of these complex patients. Three particularly important areas of postoperative care in this case were nutrition, adhesive usage, and drug choice.

**Conclusion**

This case underscores the importance of recognizing possible postoperative complications in patients with this cluster of diseases and realizing that treatment of these complications will need to be adaptive in order to address unique concerns in patients with EDS, POTS, and MCAS. Further, the complex postoperative course of this patient emphasizes how essential it is to investigate the nature of the relationship between these diseases. In the future, better understanding this disease cluster and identifying potential mechanisms linking them could lead to improved preoperative and postoperative management of these patients.

**References**


