Microcystic Lymphatic Malformation:
A case presentation and review

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ABSTRACT

Lymphatic malformations are rare but benign abnormalities of the lymphatic system. They can present anywhere in the body and range in size from millimeters to inches. Most cases are either diagnosed at birth or by 2 years of age. Approximately 60% of all lymphatic malformations are found in the head and neck with the majority of those found intra-orally. However, they can present in adulthood, indicating a possible acquired nature. When presenting for the first time in adulthood, the most common location has been found to be retroperitoneal. Many cases can be initially diagnosed with a thorough history and physical exam, however further investigation may be necessary to determine the extent of the disease. Multiple classification systems have been formed in order to improve diagnosis and treatment of each individual lesion. The most commonly used classifications are based on size and location of lesions. In general, smaller and more diffuse lesions are harder to treat and have a worse prognosis. There have been multiple attempts at finding a definitive therapy for each type of lymphatic malformation. However, there is still a debate about which method to use as the first line. For larger malformations, research seems to favor complete surgical excision, sclerotherapy, or a combination of the two. Smaller malformations have been more difficult to treat with a higher rate of complications and regrowth. A staged plan, using multiple treatment techniques including but not limited to laser therapy, surgical excision, and sclerotherapy has been shown to be efficacious. However, a more recent treatment method using radiofrequency ablation on smaller lesions has been showing promising results and may become the prominent treatment modality in the future.

Presentation of case

A 2½ year old boy was brought in to the emergency department due to spontaneous fissured, blistering, and painful tongue.

A Caucasian boy was born to a 22 year old G1P1 female at 40 weeks gestation. Labor lasted 13 hours and delivery method was vaginal and without complications. Pregnancy was significant for prolonged hyperemesis gravidarum that resulted in a 22 pound weight loss in the first trimester and 2 overnight hospitalizations for dehydration and IV fluid administration. The mother was on no medications prior to or during pregnancy other than prenatal vitamins. She did initially smoke cigarettes and engaged in light social drinking the initial first weeks before she found out she was pregnant, at which point she stopped both. At birth, a benign hemangioma was noticed covering the boy's lower lip. There were no other abnormalities. His hospital stay was uncomplicated and he was discharged home with the mother, who was breastfeeding. At 3 days of life, he developed jaundice and needed to be treated in an incubator for phototherapy in the hospital for 6 days. Afterwards, he continued to grow and remained healthy, receiving all of his vaccinations when due. When he was 2½ years old, he was visiting family when his tongue suddenly became painful. He told his mother and upon examination the posterior half of his tongue was covered in "blood blisters". He was immediately brought to the Emergency Department for further evaluation. When the physician placed pressure on the lesions with a tongue blade, they burst open as started to bleed. Unsure of the cause, the boy was sent via ambulance to a higher care pediatric facility. By that time, the bleeding had ceased and the boy was in no discomfort. The physicians at the second ER also did not know the cause of his symptoms and since it was no longer bothering him, they sent him home to follow up with his pediatrician as an outpatient. The pediatrician did not have a specific diagnosis and recommended close monitoring. After the initial episode, the boy's tongue continued to have a rough cobblestone appearance with deep fissures. It no longer hurt, but was mildly tender and enlarged when he had upper respiratory tract infections. It bled

minimally, again only during infections. The majority of the time, the lesions were not noticeable and did not seem to bother the boy. However, since they never disappeared, the mother did some research on possible causes. When the boy was 4 years old, his mother brought him to a specialist who diagnosed him with lymphatic malformation of the tongue based on history and physical exam. Since there was no discomfort or airway obstruction, it was decided that no treatment needed to be done at that time and they would continue with watchful waiting with close follow up. By the time the boy was 9 years old, he was referred to an otolaryngologist who had been treating these types of lesions with a new method. That physician first performed a laryngoscopy to visualize the extent of the disease and it was found to stop at the base of the tongue with no laryngopharyngeal or esophageal involvement. The boy was then taken to the O.R. for radiofrequency ablation under general anesthesia He was successfully extubated immediately following the procedure and had no further complications. He was initially placed in the NICU for close monitoring but only needed to stay in the hospital for 2 days before being discharged home. After the procedure, his tongue was swollen for at least 1 week. He was able to eat during that time, but only soft soothing foods such as pudding, ice cream, and yogurt. When the healing was complete, there still was a certain amount of malformation left in the middle of the posterior tongue but it was significantly reduced. Nine years post-operative, there are still lesions present, but they have not grown or spread. They will get minimally inflamed during an infection but no longer hurt or bleed. Because of this, he did not feel like he needed another treatment at this time.

INTRODUCTION

A lymphatic malformation is a subtype of a vascular malformation. It was initially grouped into this category after a study in 1982 by Mulliken and Glowacki found a histological difference between the cells and stages of growth of multiple different lesions. The classification was made up of two main groups, hemangiomas and malformations. Hemangiomas, described as lesions with increased mitotic activity and cellular proliferation, are the most common benign tumors of infancy (4). Unlike malformations, hemangiomas have a proliferative and involuting phase, at which point they may completely regress on their own. Although not specifically classified into types, the study did mention that hemangiomas can be superficial (capillary), deep (cavernous), or mixed (4). Malformations were described as structural abnormalities from errors of vascular morphogenesis, which can enlarge with changes in pressure and flow, ectasia, collateral formation, shunting, and hormonal modulation (4). These lesions were further broken down by the type of vasculature from which they arose, including capillary, venous, arterial, lymphatic, and fistulae (4).

Despite multiple speculations and attempts at understanding the pathogenesis behind these lesions, it is still fully unknown. Mainly, this is due to the incomplete understanding of the morphogenesis of the lymphatic system However, despite the developmental debate, it has been accepted that lymphatic malformations have an abnormal communication with the normal venous drainage system, which likely develops between 8-10 weeks of gestational age. In 1902, Sabin proposed that lymphatic structures arise from five primitive buds that sprout from the venous system during embryology (21). Through her intricate research, she noticed that cells budded from those sacs and spread to the periphery in a centrifugal manner, forming capillary networks throughout the body alongside the venous system. This became, and still is the single most widely accepted model for lymphogenesis (35). Alternatively, in 1910, Huntington and McClure suggested a centripetal developmental pattern where primary lymph sacs arose in the mesenchyme, independent of, but later established connections with the venous system (36*, 34). Although Sabin's theory has been more traditionally accepted, further research has been done that suggests that lymphogenesis has multiple pathways of development and could arise from a combined venous-mesenchymal origin (van der Jagt

1937 (the origin and development of the anterior lymph sacs in the sea turtle), Wiegand et al 2008 (Pathogenesis of lymphangiomas), ?van der Putte 1975 couldn't get article, 38, ***?37***).

Regardless of the development of lymphatic malformations, many researchers have also worked on different classification systems that will enable clinicians to better diagnose and treat their affected patients. They were initially grouped into different categories based on histology (***need sources for this – look at my 13***), however this classification was difficult to use in the clinical setting. Three main categories of lymphatic malformations have since been described that are relatively easy to diagnose clinically based on appearance and can help determine which type of therapy can be used (???). They consist of macrocystic, microcystic, and mixed, which is generally based on the radiographic size of the lesions but it also indicates the response achieved from certain therapies (? ***need sources for this, ? smith?***). Microcystic lesions (formerly known as lymphangioma) are measured at $< 2cm^3$ and if they are $\geq 2cm^3$ they are considered macrocystic (formerly cystic hygroma). If the lesions have both microcystic and macrocystic components, they are considered to be a mixed lymphatic malformation. Another popular staging model for lymphatic malformation was formed based on disease extent and location and includes: Stage I, unilateral infrahyoid involvement; Stage II, unilateral suprahyoid involvement; Stage III, unilateral suprahyoid and infrahyoid involvement, Stage IV, bilateral suprahyoid involvement, and Stage V, bilateral suprahyoid and infrahyoid involvement(**de Serres, couldn't get the article**). In general, the higher the stage, the more difficult to treat, and the poorer the prognosis. These two main classification systems are generally combined to provide an optimal diagnosis and treatment plan for each individual patient. Overall, it has been found that the larger macrocystic lesions are more commonly seen below the level of the mylohyoid muscle (1, 10) and microcystic malformations are seen more above the level of the mylohyoid.

Although benign, lymphatic malformations can be life threatening depending on their location and extent of involvement. These lesions have been diagnosed and treated in all areas of the body from head to toe, including retroperitoneal and mucosal The most hazardous lesions include ones of larger sizes that cause mass effects on vital organs, and lesions of mucosal involvement. Intra-oral lesions can become especially hazardous and cause dysphagia or airway obstruction. Lesions in this area also have an increased risk of recurrence after treatment, and recurrent infection. As noted above, microcystic malformations are more commonly found above the level of the mylohyoid muscle, and a great majority of these are partial to the oral cavity. The rest of this article will discuss lymphatic malformations, with special attention to those of microcystic origin located in the head and neck.

EPIDEMIOLOGY

Historically, all vascular malformations are present at birth but may not become apparent until later in development. Approximately 50% of all lymphatic malformations will be obvious at birth, and up to 90% will be diagnosed by the time the child is 2 years old. They are considered benign soft tissue tumors and occur in about 6% of the pediatric population (2). There has not been found to be any predilection to a particular gender or race. Of all diagnosed lymphatic malformations, at least 60% will be found in the head and neck. When found intra-orally, the tongue seems to be the most affected. As already noted, lesions in this area tend to be microcystic in nature. In the realm of lymphatic malformations, since lesions of the tongue seem to be the most commonly found, Wiegand et al. formed a staging system solely for malformations of the tongue in the hopes of assessing optimal treatment methods. These include: Stage I, isolated superficial microcystic lymphatic malformations of the tongue; Stage II, lesions isolated to the tongue but with muscle involvement and further subdivided into Stage IIA, involving part of the tongue, and Stage IIB, involving the entire tongue; Stage III, involvement of the tongue and floor of the mouth; and the most extensive Stave IV, lesions that involves the tongue, floor of mouth, and further cervical structures (6)

DIAGNOSIS

Microcystic lymphatic malformations can present in a variety of different ways, even when only involving the tongue. When the lesions first appear, they look like clusters of small vesicles. The vesicles contain lymphatic fluid and can occasionally range from a pink to red to blue color if capillaries burst or leak into them. The lesions range from soft and compressible to more firm and are generally not painful to touch. They may cause the patient some pain upon eating certain foods, especially spicy or citrusy items but otherwise may not even be noticeable to the patient. They may or may not bleed on initial diagnosis or during acute infection. Bleeding is self-limiting and will stop once the irritant is removed During an infection, the lesions will react similar to other lymphatic tissue and enlarge due to the increased flow of lymphatic fluid. Any bacterial of viral infection can cause enlargement of the lymphatic malformation, but upper respiratory tract infections usually cause the most inflammation. The enlargement generally decreases on its own, but it can be potentially dangerous depending on the location and extent of the disease. Other than medical concerns, these lesions can be very aesthetically unpleasing to the patient and cause much distress.

Diagnosis can be made based on thorough history and physical exam. However, extent of the disease may be more difficult to ascertain.

TREATMENT

Management of lymphatic malformations depends on the size, location, and extent of involvement. Some stage I or II lesions (based on de Serres staging) could be left for observation and watchful waiting if they are not causing any harm or obstruction. However, if symptoms occur, the extent of the involvement is more severe, or the patient finds the lesions aesthetically unpleasing, steps should be taken to determine the optimal treatment option that would best improve their symptoms. Prognostically important factors to take into consideration when deciding on type of treatment include hyoid level, laterality, age of onset, growth rate, type, depth, extent, anatomical location, potential deformity or dysfunction of lesion (12). For instance, bilateral deep lesions above the level of the hyoid will be more difficult to treat and have worse outcomes than unilateral superficial lesions, especially if below the level of the hyoid. For those who choose or need to be treated secondary to location or extent of disease, there are multiple methods that have been studied that can be performed. The most common of these include surgical resection, sclerotherapy, laser therapy, and radiofrequency ablation Other treatment types that have been tried but not studied as extensively include electrocoagulation, cryotherapy, ligation, radiotherapy, and embolization. Many times, multiple forms or number of treatments need to be performed in order to reach the desired outcome. Restricted or low grade lesions have been shown to have good results with a single treatment of surgery, laser therapy, or sclerotherapy. More diffuse or higher grade lesions will likely require two or more treatments of either the same or different methods in order to reach the desired outcome. There is still also a disagreement on timing of treatment. Many researchers and clinicians advise to wait until after 3-5 years old to treat because of possibility of regression (11). However, some suggest to treat before the age of 3 since this is before the development of facial image and memory (33). Regardless of age, if the lesion is rapidly growing, impinging on vital organs, or causing airway obstruction, a more emergent course of action must be taken.

Surgical Resection

Surgical resection has been done in both macro- and microcystic disease and can also be curative to the larger lesions. Whereas complete resection has a decreased chance for recurrence, it is not always an option (16). Due to its infiltrative nature, thin friable walls, and close proximity to cranial or facial nerves (when involving the head and neck), microcystic disease is difficult to remove completely, especially without further complications and aesthetically pleasing results. In microcystic or more diffuse macrocystic or mixed lesions, a staging method for surgical excision has shown to have the best results (11).

Multiple post-operative complications have been cited, the most common including infection, bleeding, and recurrence of the lesions. More devastating complications have included nerve palsy, muscle weakness, recurrent infections, and recurrent airway obstruction. With the majority of lesions affecting the head and neck, the most common nerve affected is the marginal mandibular branch of the facial nerve (6, 16), but cranial nerves IX – XII also seem to be vulnerable (10, 16). Intra-operative nerve injury has been found to be most associated with size and extent of the lesion (13). Partial resections can be done but have been shown to be associated with a high rate for regrowth (1, 10). Because of this, many studies have looked into the use of other treatment methods with or without surgical excision and found that there are added benefits to multi-therapy approach.

Sclerotherapy

Single, initial, or adjunct therapy for many lymphatic malformations has involved injection of the lesion with a sclerosing agent. This was initially created as a treatment for these lesions after some patients who had local infection or hemorrhage into the affected area, further causing fibrosis and scarring of the lesions and subsequent spontaneous resolution. Since then, many different agents have been tested for use in sclerotherapy, the most commonly used including pingyangmycin, bleomycin, OK-432, doxycyxline, and ethanol. Initial use of sclerotherapy was not favored because the agents used would diffuse into adjacent structures which caused more complications. Further breakdown of the surrounding skin and soft tissues also looked bad and the more diffuse fibrosis made the lesions harder to surgically excise later on. However, with further research, different agents were found that did not spread outside the lesion being directly injected. Although proven very useful and curative for macrocystic disease, sclerotherapy has been shown to be somewhat ineffective in microcystic disease due to the size of the lesions and their infiltrating behavior (1, 10, 18). However, several studies have investigated using single or multiple treatments with sclerotherapy as the sole form of treatment in microcystic disease with fair outcomes (18, 26). More commonly, sclerotherapy is used as a prejunct to more definitive therapy, or as an adjunct to an initial therapy if lesions recurred or were found to be left behind (18). Despite no reports showing complete removal and recovery of microcystic malformations with sclerotherapy, some authors still state that it should be used as first line therapy for both macrocystic and microcystic lymphangiomas due to its beneficial effect and lack of complications compared to other types of therapy (26).

The most efficacious method to use sclerotherapy includes initially aspirating as much fluid as possible from the cyst(s). A set amount of the sclerosing agent (different doses depending on agent) is then injected back into the cyst(s). Compression after injection can further aid in maximizing contact of the sclerosing agent with the affected tissues, and help reduce extravasation (17).

Types and extent of side effects vary and depend on type of agent used and include. pain in injection, edema, ulceration, induration, scarring, and recurrence when sclerotherapy is used alone (31)

Laser Surgery

Multiple types of laser therapies have also been studied and are still commonly used in localized superficial microcystic disease. It can be especially useful in the larynx and other areas of the oral mucosa that are not as amenable to other therapies. The types most commonly used include CO2 laser, Nd:YAG-laser, and pulsed-dye-laser They generally work by using fine-tuned destruction of a small area with minimized damage to adjacent structures. Because of this, there is a faster healing time compared to the previously mentioned treatment methods as well as fewer complications However, because of the high energy used, these treatments have been associated with significant thermal damage to surrounding tissues with fibrosis and scarring (14). When used alone, it has also been shown to have a high recurrence rate between 50-100% (5).

CO2 minimizes bleeding in superficial areas; Nd:YAG good for interstitial areas; Pulsed dye good for lesions right under surface of tongue (8)

Radiofrequency Ablation

The newest method of treatment reported is that of radiofrequency ablation (RFA). It works by producing a controlled increase in temperature limited to a certain region, and results in denaturation and obliteration of the specific site while causing little damage to nearby structures (17, 2). The energy dissipates quickly which is why it is able to cause little collateral damage to adjacent structures (17, 2). It is thought that this reduced thermal energy may reduce the regrowth of residual malformations and may improve wound healing (10). Also, since RFA destroys only the lymphatic malformation and affected mucosa with little residual energy damage, the tongue is allowed to heal and remucosalize on its own without any reduction in normal tongue volume or alteration in appearance (32).

There are two different methods by which someone can use radiofrequency ablation. One method inserts a bipolar probe into the affected tissue. The energy produced causes an increase in temperature in the surrounding tissue which then causes tissue destruction. The other method is also called coblation and uses energy through a conductive medium that, when in contact with the affected tissue, will cause breakage of chemical bonds and dissolution of the tissue. Along with this, the destroyed tissue can be aspirated out through the same "wand" that destroys it (10). In general, this technique originally started using high-frequency energy and usually required intubation with general anesthesia. However, a case study in 2008 paved the way to start using a low-frequency mode, which can be done in an office setting with local anesthesia (1).

DISCUSSION

The beta blocker, Propranolol, was recently recognized as a first-line treatment of infantile hemangioma due to its effect of inadvertently reducing the vascular endothelial growth factor (VEGF), which likely plays a large role in vasculogenesis. In 2013, Ozeki et al proposed that propranolol could also be used as a treatment for lymphatic malformations by also inhibiting lymphangiogenesis (24) Their study consisted of 6 patients and included both macrocystic and microcystic lesions Although some of the patients reported some subjective improvement, there were unfortunately no clinically significant responders to the treatment.

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