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A NEW CASE AND REVIEW OF CHYLOTHORAX IN GENERALIZED LYMPHATIC ANOMALY AND GORHAM-STOUT DISEASE

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ABSTRACT

Generalized lymphatic anomaly (GLA) and Gorham-Stout disease (GSD) are related diseases involving the lymphatic vasculature. Patients with these diseases frequently develop chylothorax, which can cause respiratory distress, failure, and death. Unfortunately, the optimum treatment for GLA and GSD patients with chylothorax remains unknown. Here we review 64 previously reported cases of chylothorax in GLA and GSD and describe a GLA patient with bilateral chylothorax that was treated with a pleurovenous shunt after multiple other treatments failed. Unfortunately, this shunt was not able to control the patient's effusion, and she succumbed to her disease 3 years after the shunt was placed. Interestingly, our literature review revealed that patients with left-sided effusions had better outcomes than patients with either right-sided or bilateral effusions. Taken together, our report highlights the difficulty in managing chylothorax in patients with GLA or GSD and reveals that a better understanding of the cause of chylothorax is needed so that new therapies can be developed to treat this common complication of GLA and GSD.

Keywords: Gorham-Stout disease, osteolysis, chylothorax, treatment, Denver/ pleurovenous shunt, lymphangiomatosis, lymphangiogenesis, generalized lymphatic anomaly, case, review

GLA (formerly called lymphangiomatosis) and GSD are lymphatic anomalies that have overlapping symptoms and complications. GLA is a rare disease of unknown etiology characterized by the extensive proliferation of lymphatic vessels and frequently affects bone (1). GSD is a related disease characterized by the presence of lymphatic vessels in bone and by the gradual disappearance of bone (2). Recently, these similar diseases were differentiated from one another by their pattern of bone loss. Patients with GLA display lytic lesions confined to the medullary cavity whereas patients with GSD display progressive osteolysis and loss of cortical bone (1). Although these diseases can affect any bone in the body, they most frequently affect the ribs (1). Importantly, rib involvement is associated with chylothorax. The treatment of chylothorax in GLA and GSD patients is often quite challenging and usually requires a multidisciplinary team and multiple strategies. The most common treatments for chylothorax in GLA and GSD are diet modification, thoracentesis, octreotide, pleurodesis, thoracic duct ligation, interferon, and radiation (3). These therapies are reported to have a wide range of outcomes, and there is no consensus on the best

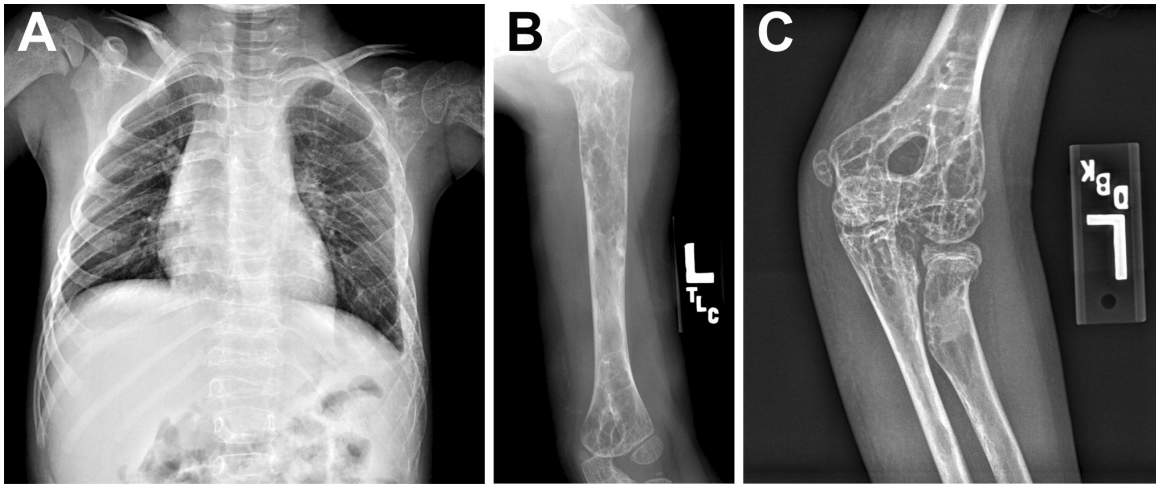


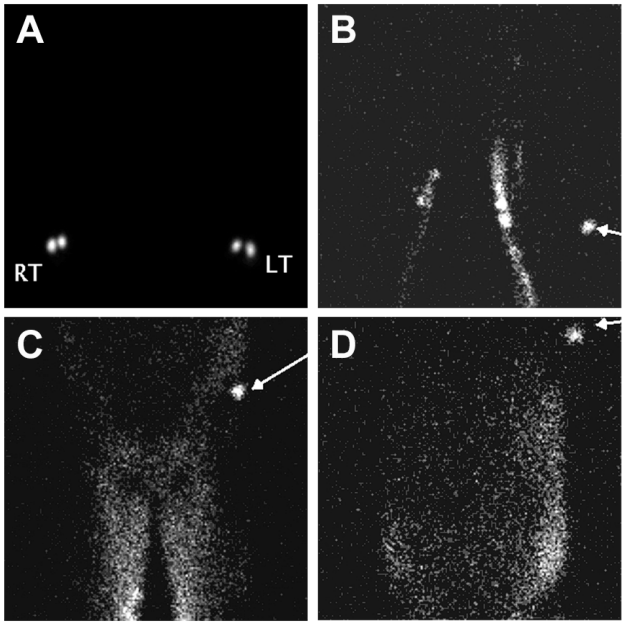
Fig. 1: Radiographs showing lytic lesions in the chest and left humerus. (A) Multiple lytic lesions are present in the ribs and right clavicle. (B,C) Radiographs showing lytic lesions in the left humerus. Importantly, cortical bone is still present in the humerus. This pattern of bone loss is more consistent with GLA than GSD.

treatment modality for chylothorax in GLA and GSD. In this report, we review the treatment of 64 previously reported cases of chylothorax in GLA and GSD and describe a new GLA patient with chylothorax that was treated with a pleurovenous shunt.

CASE PRESENTATION

A 3 year-old girl was referred to the Oncology clinic for osteopenia, back pain, and a history of fractures. Past history revealed that at 6 months of age she was noted to have an enlarged left arm and was diagnosed with a bone lesion of undetermined etiology. She was followed by Orthopedics and Nephrology but no biopsies where obtained. Due to decreased bone mineral density and a history of fractures she was started on Fosamax (alendronate, type of bisphosphonate). Medical history revealed an otherwise healthy female. A history of trauma or other disorders was absent. There was no family history of bone deformities or childhood malignancies. On physical exam she was noted to have left sided hemi-hypertrophy of the shoulder, humerus, femur, and ribs 8-12. Skin examination revealed an erythematous and blue lesion on the left inner thigh. There were decreased lung sounds at the left lower lung base. Skeletal survey revealed lytic bone lesions scattered throughout her skeletal system with greatest involvement of the left humerus and the left lower ribs. Importantly, the cortex was preserved in the affected bones (*Fig. 1*). Computed tomography of her chest revealed a moderately sized left pleural effusion and small right pleural effusion. Biopsy of the left humerus revealed fragments of trabecular bone and intramedullary soft tissue. The soft tissue fragments contained lymphatic vessels, which were described as thin-walled and abnormal in appearance. D2-40-positive vessels were present in the bone biopsy (data not shown). Given the pathological findings in combination with the radiologic bone changes, a diagnosis of Gorham-Stout disease was made. This diagnosis was later changed to GLA because the patient's pattern of bone loss was found to be more consistent with GLA than GSD.

Although at initial presentation the patient did not have respiratory distress or tachypnea, the decision to start therapy was made due to her high risk of pathologic



Fig, 2: Lymphoscintigraphy findings. (A) Initial injection of radiotracer in both feet. (B) At 7 minutes, radiotracer is observed in normal lymphatic channels in the lower legs and in the popliteal lymph nodes. Normal lymphatics are not seen superior to the distal thighs (marker at the knee, arrow). (C,D) At 90 minutes, radiotracer is seen diffusely within the soft tissues of the thighs (C, marker at the iliac crests, arrow) and along the abdominal and thoracic walls (D, marker at the shoulder, arrow).

fractures and high associated mortality from the presence of pleural effusions. Initial treatment was started with interferon subcutaneously daily and zometa (zoledronic acid, type of bisphosphonate) IV every four weeks for one year. Her bone pain improved and her pleural effusions remained stable. Six months into therapy, the dose of interferon was reduced by 35% due to liver toxicity and elevated liver enzymes. Routine imaging obtained 8 months into treatment demonstrated resolution of the pleural effusions and improvement in bone density. Therapy was completed after 12 months of treatment. Unfortunately, approximately 3 months later, she had progression of her skin lesions and steroids and interferon were restarted. Following 3 months of steroids there was no response in the size of the skin lesion and she was weaned off. She was then started on IV vincristine, and had minimal response in the size of her skin lesions. Vincristine was ultimately stopped and she was continued on single agent therapy with interferon. She completed a total of 2.5 years of interferon therapy. Ultimately, the interferon was stopped secondary to the development of hemolytic anemia and progressive bone disease.

She was then started on Thalidomide but 2 months after initiation she developed severe headaches and the decision was made to stop the medication. She continued to have bilateral pleural effusions and subcutaneous skin lesions, so she was started on Methotrexate 30 mg/m2 IV and Vinblastine 5 mg/m2 IV weekly. Approximately 2 months into therapy she developed worsening ascites and pleural effusions and was admitted to our hospital for medical management. Lymphoscintigraphy was performed during admission and demonstrated grossly abnormal lymphatic drainage (*Fig. 2*). No normal lymphatic channels were seen above the level

of the knee. The radiopharmaceutical agent migrated through the subcutaneous tissue of the abdominal cavity and into the chest. She was started on intravenous octreotide and a low fat diet for management of her effusions but had minimal clinical response. Rapamycin (mTOR inhibitor) was started. While she initially had clinical improvement on rapamycin, her computed tomography scans demonstrated persistent pleural effusions. She ultimately developed tachypnea and profound abdominal ascites 3 months into therapy and rapamycin was stopped due to disease progression.

She was re-admitted to our hospital for medical management of the pleural effusions. Her symptoms worsened rapidly, and she developed respiratory distress and progressive dyspnea. For symptomatic relief, she had bilateral chest tubes placed which drained ~4-10 liters of chylous effusions per day. She was restarted on interferon and tried on Avastin (bevacizumab, anti-VEGF-A antibody). Multiple attempts of pleurodesis and sclerotherapy with doxycycline were completed. While these interventions temporarily decreased her chest tube output to 2-4 liters per day, the effect did not persist and her chylous effusions ultimately increased within weeks. Due to her high volume of chylous output and the associated difficulty in managing her fluid balance, the decision was made to place a pleurovenous shunt. Following this procedure her pleural effusions improved rapidly. Six days following surgery, she was discharged home, stable on room air. Throughout the following 3 years she remained without pleural effusions or respiratory complications. She was intermittently admitted to the hospital for bone infections and/or fractures. She did require replacement of the pleurovenous shunt on one occasion but otherwise did not require chest tube placement or drainage of pleural fluid.

Unfortunately, 3 years after placement of the pleurovenous shunt, her disease progressed with worsening anemia and coagulopathy. She was again admitted and found to have a functioning pleurovenous shunt and minimal pleural effusions; however, she had worsening abdominal ascites and extremity swelling. She was restarted on interferon, steroids and vincristine. Nonetheless, her disease progressed and she developed pulmonary edema, dyspnea and increasing collections of malformed vessels in her abdomen, which accumulated large amounts of fluid within them. Sclerotherapy was attempted to the flank and led to the removal of large volumes of blood and chylous fluid. The fluid quickly reaccumulated despite all the interventions attempted. She continued to have profound electrolyte and hematologic derangements and ultimately developed worsening mental status, increasing respiratory acidosis and elevated creatinine and liver enzymes concerning for multi-organ failure. Ultimately she was placed on comfort care and passed away.

CONCLUSIONS

Over the past 2 decades, substantial progress has been made in the study of the lymphatic vasculature. Despite this progress, many questions still exist surrounding the etiology and treatment of lymphatic anomalies such as GLA and GSD. Our challenging case of GLA, and the paucity of information on chylothorax in GLA and GSD, prompted us to review the literature on these diseases to identify factors associated with the development of chylothorax and to determine the efficacy of various treatments for chylothorax in GLA/GSD patients. We chose to include GSD in our literature search because the lymphatic abnormalities in GSD are very similar to GLA and because GLA cases can be misdiagnosed as GSD, as was the case with our patient. Through an extensive literature search, we were able to find descriptions for 64 cases of GLA/GSD with bone involvement and chylothorax *(Tables 1 and 2*) (4-58). The effusion was reported to be left-sided, right-sided, or bilateral in 17, 18, and 23

TABLE 1
Reported Cases of Generalized Lymphatic Anomaly (GLA) with Chylothorax

Reference	Reported Diagnosis	Sex	Age Diagnosed (yr)	Bones Involved	Chylothorax	Signs/ Symptoms	Pleurodesis	Thoracic Duct Ligation	Interferon	Radiation	Outcome
Alvarez et al., 2004.	GLA	Male	8	Vertebrae	YES - Bilateral	Cough, Mediastinal Mass	NO	NO	YES	YES	Died/8 yr
Konez et al., 2000.	GLA	Female	9	Vertebrae, Ribs, Sternum	YES - Right-Sided	Dyspnea	NO	NO	NO	NO	NR
Berberich et al., 1975.	GLA	Male	3	Ribs, Femurs, Tibia	YES - Bilateral	Cough, Weight loss	NO	YES	NO	NO	Survived
Bhatti et al., 1985.	GLA	Male	15	Skull, Ribs, Scapula, Pelvis, Femurs, Vertebrae	YES - Bilateral	Shortness of breath	NO	YES	NO	NO	Survived
Canil et al., 1994.	GLA	Male	12	Ribs, Scapula, Clavicle	YES - Left-Sided	Dyspnea, Pain	NO	NO	NO	NO	Survived
Dunkelman et al., 1989.	GLA	Male	9 months	Femur, Humerus, Ribs	YES - Left-Sided	Tachypnea	YES	YES	NO	NO	Survived
Harada et al., 1994.	GLA	Female	5	Humerus	YES - Left-Sided	Cough, Fever	NO	YES	NO	NO	Survived
Maki et al., 1999.	GLA	Male	12	Vertebrae, Ribs	YES - Left-Sided	Pain	NO	NO	YES	NO	Survived
Pauzner et al., 2007.	GLA	Female	46	Pelvis, Vertebrae	YES - Not Specified	NR	NO	NO	YES	NO	Survived
Reinhardt et al., 1997.	GLA	Male	12	Humerus, Scapula, Pelvis, Skull, Vertebrae	YES - Left-Sided	Dyspnea, Pain	NO	NO	YES	NO	Survived
Timke et al., 2007.	GLA	Male	11	Vertebrae	YES - Left-Sided	Dyspnea, Pain	YES	NO	YES	NO	Survived
Watts et al., 1982.	GLA	Female	28	Pelvis, Ribs, Tibia	YES - Bilateral	Recurring Chylothorax	NO	YES	NO	NO	Survived
Wong et al., 2008.	GLA	Female	6	Vertebrae, Femur, Humerus	YES - Bilateral	Shortness of breath, Fever, Mediastinal Mass	NR	NR	NR	NR	Survived
Yeager et al., 2008.	GLA	Female	7	Vertebrae, Ribs	YES - Bilateral	Cough, Dyspnea	YES	YES	YES	NO	Survived

TABLE 2
Reported Cases of Gorham-Stout Disease (GSD) with Chylothorax

Reference	Reported Diagnosis	Sex	Age Diag-nosed (yr)	Bones Involved	Chylo-thorax	Signs/ Symptoms	Pleuro-desis	Thoracic Duct Ligation	Inter-feron	Radia-tion	Outcome
Atalabi et al., 2008.	GSD	Female	4	Vertebrae, Ribs, Pelvis, Femur	YES - Bilateral	Fracture	NO	NO	NO	NO	Died/18 yr
Boyle et al., 2008.	GSD	Male	17	Sternum, Clavicle, Rib	YES - Bilateral	Dyspnea	YES	YES	NO	YES	Died/17 yr
Brodszki et al., 2011.	GSD	Male	2	Vertebrae, Pelvis, Clavicle	YES - Right-Sided	NR	YES	YES	YES	YES	Survived
Brodszki et al., 2011.	GSD	Female	4	Vertebrae, Humerus, Femur, Pelvis, Sacrum	YES - Bilateral	NR	NO	NO	YES	YES	Survived
Choma et al., 1987.	GSD	Male	16	Scapula, Clavicle, Humerus, Ribs	YES - Right-Sided	Pain, Dyspnea	NO	YES	NO	YES	Died/27 yr
Colucci et al., 2006.	GSD	Female	40	Ribs, Clavicle, Vertebrae, Scapula, Humerus	YES - Not Specified	NR	NO	NO	NO	NO	NR
De Smet et al., 2010.	GSD	Male	8	Ribs, Clavicle	YES - Bilateral	Dyspnea	NO	NO	YES	NO	Survived
Deveci et al., 2011.	GSD	Male	6	Ribs, Cranium, Vertebrae, Humerus, Femur	YES - Bilateral	Dyspnea	NO	YES	YES	NO	Died/6 yr
Duffy et al., 2005.	GSD	Female	31	Scapula, Ribs, Vertebrae	YES - Not Specified	Dyspnea	YES	NO	NO	YES	Survived
Ellis and Adams 1971.	GSD	Female	55	Vertebrae, Mandible, Maxilla	YES - Right-Sided	NR	NO	NO	NO	NO	*Died/72 yr
Fontanesi 2003.	GSD	Male	21	Humerus	YES - Right-Sided	Fracture	NO	NO	NO	YES	Survived
Fujiu et al., 2002.	GSD	Male	15	Scapula, Clavicle, Humerus, Sternum, Ribs	YES - Bilateral	Pleural Effusion	NO	YES	NO	NO	Died/15 yr
Girn et al., 2006.	GSD	Female	2	Skull, Spine, Ribs, Pelvis, Femur	YES - Bilateral	Headache	NO	NO	NO	YES	Died/8 yr
Gorham et al., 1954.	GSD	Male	16	Clavicle, Scapula, Ribs, Humerus, Vertebrae	YES - Right-Sided	Pain, Deformity	NO	NO	NO	NO	Died/18 yr
Grunewald et al., 2010.	GSD	Male	2.5	Sternum, Clavicle, Ribs	YES - Not Specified	Fracture	NO	NO	YES	NO	Survived

Reference	Reported Diagnosis	Sex	Age Diag-nosed (yr)	Bones Involved	Chylo-thorax	Signs/ Symptoms	Pleuro-desis	Thoracic Duct Ligation	Inter-feron	Radia-tion	Outcome
Hagberg et al., 1997.	GSD	Male	19	Clavicle, Ribs, Vertebrae	YES - Left-Sided	Pain	NO	NO	YES	YES	Survived
Hagerndoorn et al., 2006.	GSD	Male	17	Ribs, Vertebrae	YES - Right-Sided	Pain, Dyspnea	YES	NO	YES	NO	Died/23 yr
Jones et al., 1958.	GSD	Male	23	Clavicle, Ribs, Scapula	YES - Bilateral	Weakness, Dyspnea	NO	NO	NO	NO	Died/28 yr
Kose et al., 2009.	GSD	Female	9	Clavicle, Vertebrae, Sternum, Sacrum, Ribs	YES - Right-Sided	Pain, Dyspnea	NO	YES	YES	YES	Survived
Kotecha et al., 2012.	GSD	Female	9	Ribs, Scapula, Vertebrae, Pelvis, Femur, Tibia, Fibula, Radius, Ulna	YES - Right-Sided	NR	NO	NO	NO	NO	NR
Kotecha et al., 2012.	GSD	Male	12	Ribs, Vertebrae, Fibula	YES - Bilateral	NR	NO	NO	NO	NO	NR
Kotecha et al., 2012.	GSD	Female	13	Ribs, Scapula, Vertebrae, Pelvis, Humerus, Tibia, Fibula, Tarsals	YES - Bilateral	NR	NO	NO	NO	NO	NR
Kotecha et al., 2012.	GSD	Male	14	Ribs, Scapula, Clavicle, Vertebrae	YES - Bilateral	NR	NO	NO	NO	NO	NR
Kuriyama et al., 2010.	GSD	Female	16	Ribs	YES - Left-Sided	Pain, Dyspnea	NO	NO	NO	NO	Survived
Kyllonen 1967.	GSD	Male	16	Ribs	YES - Right-Sided	Pain, Dyspnea	NO	NO	NO	YES	Survived
Lee et al., 2002.	GSD	Female	25	Ribs, Vertebrae	YES - Right-Sided	Dyspnea	YES	NO	NO	YES	Survived
Lee et al., 2003.	GSD	Female	7 months	Mandible, Skull, Vertebrae	YES - Right-Sided	Lymphatic Malformati on	NO	NO	NO	NO	*Died/6 yr
Lee et al., 2003.	GSD	Female	9	Skull	YES - Not Specified	Lymphatic Malformati on	NO	NO	NO	YES	Died/14 yr
Mawk et al., 1997.	GSD	Male	6	Clavicle, Cervicle Vertebrae, Skull	YES - Not Specified	NR	YES	YES	NO	YES	Survived
McNeil et al., 1996.	GSD	Male	21	Ribs, Vertebrae	YES - Right-Sided	Pain, Dyspnea	NO	NO	NO	YES	Survived
Miller 2002.	GSD	Male	2	Vertebrae	YES - Right-Sided	Dyspnea	NO	YES	NO	NO	*Died/4 yr
Okafuji et al., 2005.	GSD	Male	29	Ribs	YES - Left-Sided	Dyspnea	NO	NO	NO	NO	Survived

Reference	Reported Diagnosis	Sex	Age Diagnosed (yr)	Bones Involved	Chylothorax	Signs/ Symptoms	Pleurodesis	Thoracic Duct Ligation	Interferon	Radiation	Outcome
Patrick 1976.	GSD	Male	28	Clavicle, Ribs, Vertebrae	YES - Left-Sided	Pain	YES	NO	NO	NO	Survived
Pedicelli et al., 1984.	GSD	Female	18	Scapula, Humerus, Clavicle	YES - Left-Sided	Pain, Dyspnea	NO	NO	NO	NO	NR
Pfleger et al., 2006.	GSD	Male	18	Vertebrae, Ribs, Scapula, Humerus, Pelvis, Femur	YES - Left-Sided	Dyspnea	YES	YES	YES	YES	Survived
Plasswilm et al., 1998.	GSD	Male	19	Ribs	YES - Right-Sided	Pain, Dyspnea	NO	YES	NO	YES	Survived
Riantawan et al., 1996.	GSD	Male	27	Clavicle, Ribs, Scapula, Vertebrae	YES - Bilateral	Dyspnea	NO	NO	NO	NO	Died/27 yr
Seok et al., 2010.	GSD	Male	14	Ribs, Vertebrae	YES - Right-Sided	Dyspnea	NO	YES	NO	YES	Survived
Situma et al., 2013.	GSD	Male	10	Femur, Ilium, Pubis	YES - Bilateral	Lymphatic Malformation	YES	YES	NO	NO	Died/12 yr
Suero Molina et al., 2014.	GSD	Male	13	Vertebrae	YES - Left-Sided	NR	YES	NO	YES	NO	Survived
Takahashi et al., 2005.	GSD	Female	2	Femur, Ribs, Vertebrae	YES - Left-Sided	NR	YES	NO	YES	NO	Survived
Tie et al., 1994.	GSD	Male	26	Ribs	YES - Bilateral	Pain	YES	NO	NO	YES	Died/30 yr
Tie et al., 1994.	GSD	Male	18	Scapula, Clavicle, Humerus, Ribs, Tibia, Femur	YES - Left-Sided	Pain, Dyspnea	NO	YES	NO	NO	Survived
Venkatramani et al., 2011.	GSD	Male	12	Cervical and Thoracic Vertebrae, Ribs	YES - Bilateral	Weakness	NO	YES	NO	YES	Died/17 yr
Venkatramani et al., 2011.	GSD	Female	13	Scapula, Humerus, Femur, Tibia, Vertebrae	YES - Left-Sided	Pain	NO	NO	NO	NO	Survived
Venkatramani et al., 2011.	GSD	Male	14	Vertebrae, Ribs	YES - Bilateral	Weakness	NO	NO	NO	NO	Survived
Yildiz et al., 2009.	GSD	Male	6	Ribs	YES - Bilateral	Dyspnea	NO	NO	NO	NO	NR
Yoo et al., 2002.	GSD	Female	25	Ribs, Vertebrae	YES - Right-Sided	Pain, Dyspnea	NO	NO	NO	YES	Survived
Yoo et al., 2002.	GSD	Male	38	Clavicle, Sternum	YES - Left-Sided	Pain	NO	NO	NO	YES	Survived
Young et al., 1983.	GSD	Male	27	Vertebrae, Ribs	YES - Right-Sided	NR	NO	YES	NO	NO	Survived

patients, respectively. Detailed information on the location of the chylous pleural effusion was not available for 6 patients. The median age of diagnosis for GLA/GSD patients with chylothorax was 15 years (range 7 months to 55 years) and pain and dyspnea were the most common initial presenting symptoms (*Tables 1 and 2*). Importantly, 90% (58/64) of GLA/GSD patients with chylothorax had spine and/or rib involvement (*Tables 1 and 2*). These findings further support that spine and/or rib involvement is a major risk factor for the development of chylothorax.

The cause of chylothorax in GLA and GSD is unknown. Several investigators have used lymphangiography to characterize the anatomy of the lymphatic system and to identify leaks in lymphatic vessels in GLA/GSD patients. Tie and colleagues reported that a large network of irregular lymphatic vessels was present in their patient and that contrast material leaked from these vessels into the thoracic cavity (23). Patrick reported that the upper part of the thoracic duct was irregular and displayed a "lymphangioma-like" appearance in a GSD patient. Chyle appeared to leak from this structure into the pleural cavity of the patient (41). Pedicelli and colleagues reported that multiple lymphatic cysts were present in the mediastinum of a patient with chylothorax and that multiple bones in their patient filled with contrast material (42). Other investigators have also reported that contrast material can fill and persist in affected bones in patients with GLA/GSD (26,59,60). These findings demonstrate that there are severe morphological changes to lymphatic vessels in the thoracic cavity in GLA/GSD patients and suggest that chylothorax is caused by irregular anatomy of the lymphatic vasculature. Additionally, these reports show that lymphatic vessels in affected bones are in communication with lymphatic vessels located outside of bones.

Chylothorax is a potentially life-threatening comorbidity in GLA and GSD. We found that 28.3% (15/53) of GLA/GSD patients with chylothorax died as a result of their disease (*Tables 1 and 2*). We also observed a significant difference in survival between patients with a unilateral effusion (3 deaths/26 no deaths) and patients with a bilateral effusion (11 deaths/8 no deaths) ($P = 0.0008$; Fisher's exact test). Interestingly, our analysis also revealed that 0% (0/16) of patients with a left-sided effusion, 23% (3/13) of patients with a right-sided effusion, and 57.8% (11/19) of patients with a bilateral effusion succumbed to their disease (*Tables 1 and 2*). These results suggest that patients with a left-sided effusion have a better prognosis than patients with either a right-sided or bilateral effusion. The difference in outcome may be related to the location of the leak and the ability of collateral pathways to form and drain lymph. It is worth noting that a limitation of our study is that our data come from case reports, which differ in their length of time of follow-up. Future studies using data collected from patient registries/databases could be used to develop more accurate mortality rates for GLA and GSD patients with chylothorax.

Various treatments are used to manage chylothorax in GLA and GSD. Pleurodesis, thoracic duct ligation, interferon, and radiation are therapies that are frequently used to treat chylothorax in GLA and GSD. We found that 26.6% (4/15) of patients treated by pleurodesis, 30% (6/20) of patients treated by ligation of the thoracic duct, 17.6% (3/17) of patients treated with interferon, and 31.8% (7/22) of patients treated with radiation succumbed to their disease (*Tables 1 and 2*). The decision to place a pleurovenous shunt in our patient was made after she failed to respond to several different therapies. This shunt provided temporary relief to our patient and may represent a way to prolong the survival of patients who do not respond to other therapies.

In conclusion, our case and review of the literature demonstrates that new therapies are desperately needed to treat GLA and GSD. Future studies focused on identifying

the genetic underpinnings of GLA and GSD could lead to the identification of new therapeutic targets for these diseases. Additionally, new forms of lymphatic imaging (e.g., dynamic contrast MR lymphangiography for MR guided interventional therapy) may make it possible to identify the cause of chylothorax in GLA and GSD patients. Together, these advances may yield new therapeutic strategies to treat GLA and GSD and improve the outcome of patients with chylothorax.

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