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Neonatal Generalized Lymphatic Anomaly with Skin Involvement

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Generalized lymphatic anomaly (GLA) is a rare congenital disorder of lymphatic development, presenting with multiple lymphatic malformations in different organs and tissues. Here, we present a case of a female neonate prenatally diagnosed with foetal hydrops and a mediastinal cystic lymphatic malformation that showed postnatal expansive and infiltrative growth into the major airways, compromising mechanical ventilation and further management of the neonate. Complications that arose during surgical treatment of mediastinal structures led to the patient's death. Lymphatic malformations were also noted in the skin at birth. Furthermore, a skin biopsy performed immediately after birth and the autopsy revealed an extremely rare diagnosis of combined macrocystic and microcystic forms of GLA with skin involvement.

Keywords: Generalized lymphatic malformation, Lymphangioma, Lymphatic abnormalities, Neonate, Skin

INTRODUCTION

Generalized lymphatic anomaly (GLA), formerly known as lymphangiomatosis, is a very rare congenital disorder that arises through anomalous embryogenesis of the lymphatic system. It is characterised by the presence of multiple lymphatic malformations (LMs), infiltrating different tissues and organs at various extents. It primarily affects abdominal and thoracic viscera and bones, with a coincident involvement of the skin and soft tissue of the retroperitoneum and mediastinum[1-4]. GLA occurs without sex predilection, with the age of presentation ranging from neonates up to 80 years. However, it predominately presents in late childhood[4]. Diagnosis can be challenging because of the broad spectrum of symptoms, anatomic locations, and imaging features[5,6]. Despite emerging novel medical therapies, the prognosis is dependent on the extent of the disease. A poor prognosis is associated with vital organs involvement[1-3,5].

Here, we present a female neonate prenatally diagnosed with foetal hydrops and a large mediastinal cystic mass, who was born with several well-circumscribed, bullous skin lesions in the thigh, groin, gluteal and chest wall regions.

CASE REPORT

A 30-year-old female, gravida 0, para 0, was referred to Mother and Child Health Institute of Serbia at 29 gestational weeks (g.w.) for foetal magnetic resonance imaging (MRI) evaluation as polyhydramnios, foetal mediastinal tumor mass, and ascites were detected on ultrasound. MRI demonstrated an expansive cystic mass in the upper and middle parts of the posterior mediastinum, extending to the neck. Bilateral pleural effusion, ascites, and subcutaneous oedema were consistent with the diagnosis of foetal hydrops (Fig. 1A). The female foetus was delivered by elective caesarean at 32.6 g.w. Her birth weight

was 2,350 g, body length was 44 cm, head circumference was 32 cm, and Apgar score was 5/6. The neonate developed signs of respiratory distress immediately after birth, requiring intubation and ventilation. Furosemide diuretic therapy was also administered. Several well-circumscribed, bullous skin lesions were visible in the thigh, groin, gluteal region, and chest wall (Fig. 2A). A full body skeleton X-ray did not show any lesions affecting the bones.

Histopathological analysis of a skin biopsy from the thigh lesion revealed cystic, irregularly shaped, thin-walled, dermal, and subcutaneous vascular channels lined by non-atypical endothelial cells that were immunoreactive for CD31 and podoplanin (D2-40), confirming their lymphatic differentiation (Fig. 2C, D). The remaining skin lesions became flattened in the following days, with a slightly uneven surface and pale purple color (Fig. 2B).

The computed tomography (CT) scan confirmed a prenatally diagnosed cystic mediastinal mass. Flexible bronchoscopy revealed a non-pulsatile mass compressing and obstructing the left lower lobe bronchus. A few days later, the chest X-ray

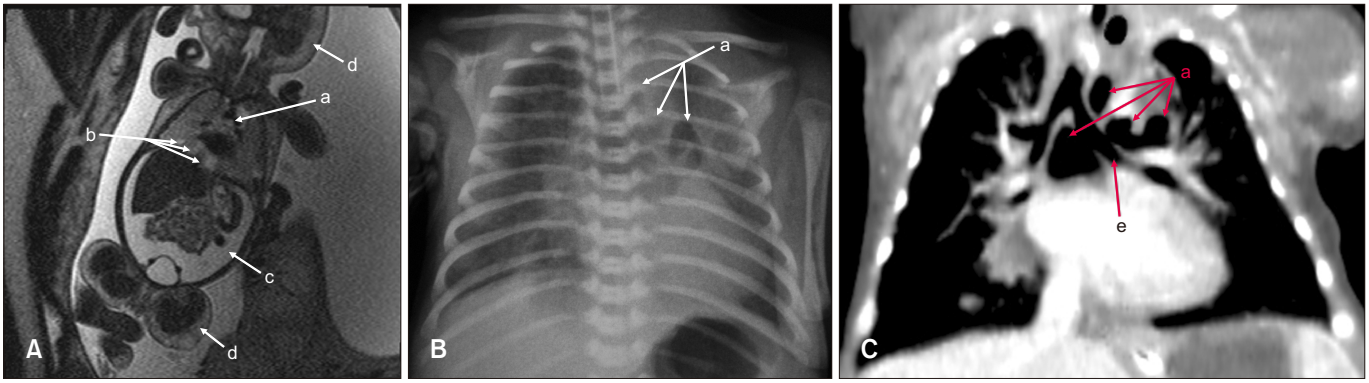

Fig. 1. (A) The fetal magnetic resonance imaging showing hydropic fetus. (B) Neonatal chest X-ray showing air-fluid level in the mediastinal cystic lesion. (C) Thoracic computed tomography scan. a: multicystic mediastinal mass, b: intrapulmonary subpleular lesions, c: ascites, d: subcutaneous oedema, e: left main bronchus.

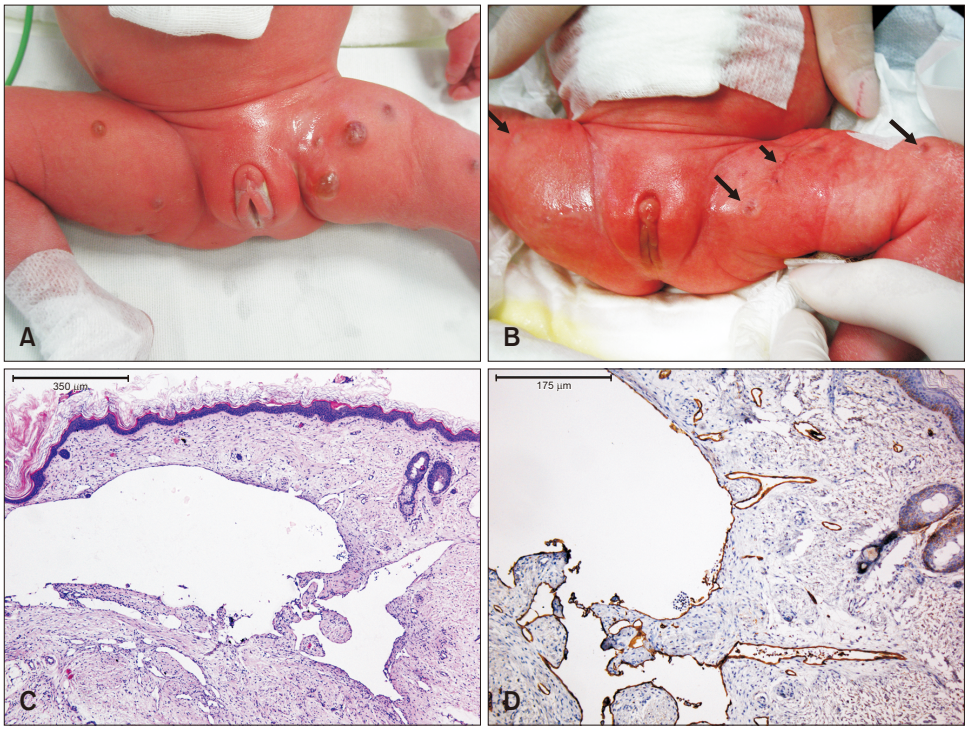

Fig. 2. (A) The bullous skin lesions in both thighs and groins. (B) Two days after excision of one skin lesion (short arrows indicate surgical scar), the remaining bullous lesions (long arrow) are flattened, collapsed, a slightly uneven surface, and a pale-purple color. (C) Irregularly shaped, thin-walled, cystic, dermal and subcutaneous vascular channels (H&E, ×5). (D) Podoplanin (D2-40) immunopositivity indicates that endothelial lining of cystic spaces is lymphatic in nature (H&E, ×10).

revealed air within the mediastinal cyst (Fig. 1B, C). Repeated bronchoscopy revealed yellowish lymph-like fluid within the bronchial lumen, indicating emerging pathological communication between the bronchus and the mediastinal cyst. A surgical operation was performed to explore the lesion and potentially close this pathological communication. A large mediastinal cyst was found to have a partly necrotic wall firmly fused within the wall of the distal trachea and main bronchi. The attempt to close the small defect between the cyst and tracheal lumen led to fatal profound bleeding during the operation.

During the autopsy, a large collapsed mediastinal multilocular cyst with a thin wall and smooth inner surface was found. The lumen of the cyst appeared to communicate with the lumen of the distal part of the trachea through an irregular slit-like defect measuring 1.5 cm in diameter. Histopathological analysis of the cystic mass showed a fibrous wall of variable thickness. The surrounding fibrous and fatty tissues were diffusely infiltrated by dilated and anastomosing lymphatics, which were also found throughout the walls of the trachea,

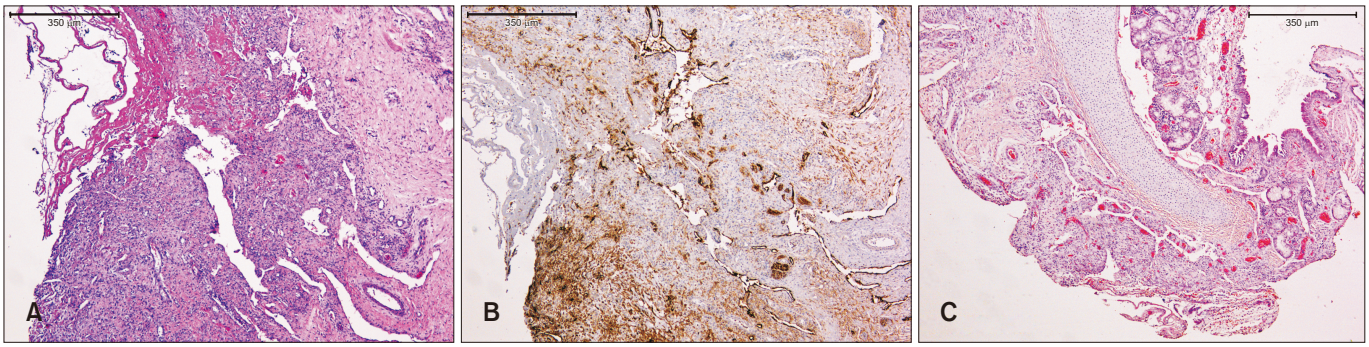

Fig. 3. The mixed macro and microcystic mediatinal lesions. (A) A segment of the large mediastinal cyst wall partially coated with fibrin. Slit-like, irregularly shaped, vascular channels spread through the wall of the cyst to the surrounding mediastinal connective tissue (H&E, ×5). (B) The D2-40 immunopositivity of the endothelial lining confirms the presence of abnormal lymphatic vessels (H&E, ×5). (C) Malformed lymphatic vessels are seen in the tracheal wall on the outer and inner side of the cartilage ring (H&E, ×5).

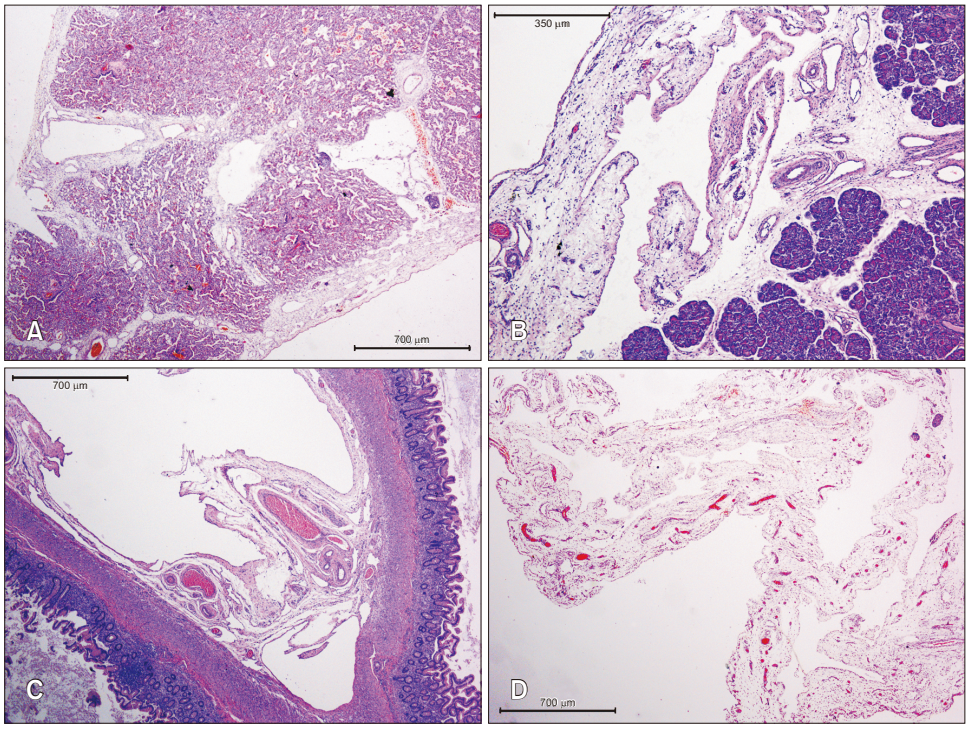

Fig. 4. The microcystic component of the generalized lymphatic malformation can be seen in the pleural and lung interstitium (H&E, ×2.5) (A), peripancreatic soft tissue (H&E, ×5) (B), mesocolon fatty tissue (H&E, ×2.5) (C), and omentum (H&E, ×2.5) (D).

bronchi, and oesophagus (Fig. 3). Malformed lymphatic vessels were diffusely present in the pleura and interstitium of both the lungs (Fig. 4A). Small areas of microcystic LMs were found in the mesocolon, gallbladder serosa, and bilateral periadrenal/peripancreatic soft tissue (Fig. 4B~D). The flattened skin lesions had identical histology to previously biopsied skin lesions. No bone lesions were noted after assessing several sections of the ribs. Immunohistochemistry for CD31 and D2-40 confirmed the lymphatic endothelial nature of the malformed vessels (Fig. 2D, 3B).

Based on the autopsy and skin biopsy, the diagnosis of combined macrocystic and microcystic form of GLA was established.

We received the patient's consent form about publishing all photographic materials.

DISCUSSION

According to the International Society for the Study of Vascular Anomalies (ISSVA) classification, GLA, formerly called generalized /diffuse lymphangiomatosis, is an extensive form of LM characterised by diffuse and/or multifocal involvement of organs and tissues[1-3,7]. GLA is part of a group of systemic LMs that also include Gorham–Stout disease (GSD) and Kaposiform lymphangiomatosis (KL)[5,8]. These entities share multiple overlapping features. However, in our patient, there was no bone involvement or evidence of Kaposiform cellular proliferation, and the macrocystic component of the mediastinal lesion was a striking clinical finding. Therefore, the diagnosis of GSD or KL is unlikely based on imaging and microscopic analysis[5,8-10]. However, during the autopsy, it was not possible to rule out a central conducting lymphatic anomaly (CCLA), a recently defined and poorly delineated entity, which is classified as channel-type LM by ISSVA[2,5,10-12]. CCLA can only be diagnosed via lymphoscintigraphy and dynamic contrast magnetic resonance lymphangiography[10-12], neither of which were performed. Although the distribution of LM in our patient did not follow the course of orthotopic lymphatic channels, which is a characteristic of CCLA[11], we cannot completely rule out the possibility that lesions were of the CCLA type.

Although, approximately one-third of the 35 GLA cases reported in the series of Ozeki et al.[8] were diagnosed in patients aged less than 1 year, after an extensive literature search, only a few published cases of GLA in newborns were found.

LMs of the chest have rarely been reported in neonates[13,14]. Unlike the lesions in our patient, LMs of the chest lesions usually remain asymptomatic for years. Typical proliferation of multiple lymphatic channels with pathological communication between the mediastinal cyst, trachea and main bronchi prompted urgent surgery in our patient.

To the best of our knowledge, macroscopically visible cutaneous involvement of GLA has only been reported in a few cases presented in the neonatal period[13,15,16]. Both patients presented by Thomas et al.[13] and Dutheil et al.[14] were diagnosed with chylothorax and interstitial lung thickening, consistent with pulmonary lymphangiectasia. The first neonate had LMs in the bilateral parietal region of the scalp[15]. The second patient had multiple bilateral, subcutaneous LMs in the axillae, neck, and groin and smaller lesions in the abdomen, right thigh, and back[16]. The first of the two patients reported by Mordehai et al.[15] were also antenatally diagnosed as having macrocystic LM of the right axilla. In all the three neonates[13,15,16], cutaneous LMs were combined with LMs in other anatomic locations and/or combined with chylothorax, thus representing GLA.

Microcystic LMs in the skin are traditionally called lymphangioma circumscriptum (LC). LCs present as vesicle-like lesions assembled in a plaque[1,17,18]. They are the result of increased intraluminal pressure in sequestered cutaneous lymphatic vessels and can occasionally present as blebs clinically[17,18]. The bullous-like appearance of cutaneous LM in our patient was identified as the cutaneous manifestation of GLA in Dutheil et al.'s patient[14], while the appearance of the lesions in the scalp in Thomas et al.'s patient[13] resembled a bunch of grapes. The flattening of the lesions in our patient was likely due to the collapse of cystic structures associated with a decline in intraluminal lymph pressure after treatment with diuretics.

Different treatment modalities have been proposed for GLA—observation, surgery, radiotherapy, sclerotherapy, embolisation, and pharmacotherapy. Current pharmacotherapeutic options include interferon, propranolol, corticosteroids, and more recently, the mTOR inhibitor sirolimus[1,3,4,6,10]. The infiltrative growth and extension of the disease in GLA makes it impossible to completely excise the lesions. The overall prognosis is poor, especially in patients with thoracic disease[1,3,4,6]. However, the outcome can improve in patients treated with mTOR inhibitors[6].

To the best our knowledge, this is the first well-documented case of a neonate who was diagnosed prenatally and later his-

topathologically confirmed to have combined macrocystic and microcystic GLA involving the skin, along with several chest and abdominal soft tissue structures and visceral organs.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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