

## Primary Lymphoedema at an Unusual Location Triggered by Nephrotic Syndrome

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### Abstract

**Introduction:** Lymphoedema results from impaired lymphatic transport leading to the pathologic accumulation of protein-rich lymphatic fluid in the interstitial space, most commonly in the extremities. Primary lymphoedema, a developmental abnormality of the lymphatic system, may become evident later in life when a triggering event exceeds the capacity of normal lymphatic flow. **Clinical Picture:** We present a 3-year-old nephrotic syndrome patient with an unusual localisation for primary lymphoedema. **Treatment and Outcome:** The patient was treated with conservative approach and she was cured. **Conclusion:** In this particular case, lymphoedema developed at an unusual localisation, which has not been recorded before.

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**Key words:** Childhood, Conservative treatment

### Introduction

Lymphatic system returns proteins, lipids and accompanying water from the interstitium to the venous circulation near the subclavian vein-internal jugular vein junction, bilaterally. Lymphoedema results from impaired lymphatic transport leading to the pathologic accumulation of protein-rich lymphatic fluid in the interstitium, most commonly in the extremities.<sup>1</sup> Lymphoedema may be classified as primary or secondary, based on underlying aetiology. Primary lymphoedema, a developmental abnormality of the lymphatic system, not always clinically evident at birth, may become evident later in life when a triggering event or worsening of the condition causes the lymphatic transport capacity to exceed the volume of interstitial fluid formation, causing the patient to be unable to maintain normal lymphatic flow.<sup>2,3</sup>

In this article, we present a 3-year-old nephrotic syndrome patient with an unusual localisation for primary lymphoedema, which had not been reported before, and cured with conservative approach.

### Case Report

A 3-year-old girl admitted with the complaint of oedema at eye lids and abdomen, decrease in urine amount and fatigue for the last 2 to 3 days. It was learnt from her parents that the child was completely healthy until 2 weeks ago when

she had an upper respiratory tract infection and had not received any medication during this illness.

Physical examination on admission revealed palpebral and pretibial 3+ oedema and ascites, blood pressure of 105/65 mmHg (<90p); rest of the vital findings and organ system examinations were normal.

Among laboratory examinations complete blood count was normal, erythrocyte sedimentation rate (ESR) was 58 mm/h, C-reactive protein (CRP) was negative, and ASO was 600 Todd Unite. Rheumatoid factor (RF), ANA, Anti-ds DNA were found to be negative. Biochemical examination revealed: BUN: 10 mg/dL, creatinine: 0.34 mg/dL, total protein: 3 g/dL, albumin: 0.9 g/dL, total cholesterol: 437 mg/dL and triglyceride: 788 mg/dL. Serum electrolytes were normal. Serum C3 [1.08 g/L (N: 0.79-1.52)], C4 [0.33 g/L (N: 0.14-0.45)], IgG, IgM and IgA levels were within normal limits. In urine examination: density was found to be 1012, pH 6, and protein as 3+. Microscopical examination was normal while protein excretion was calculated as 371 mg/m<sup>2</sup>/h.

Human albumin (1 g/kg) and furosemide (1 mg/kg) was applied to the patient as she had diffuse oedema, hypoalbuminaemia and decreased diuresis to less than 1 mL/kg/h. The patient was accepted as minimal change disease at first sight without performing renal biopsy, as her oedema decreased after these. Daily prednisolone therapy

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Fig. 1. Localised firm puffiness developed at right submandibular region of nephrotic syndrome patient, during nephrotic syndrome treatment.

at a dosage of 2 mg/kg with supplementary drugs (Ca<sup>++</sup>, vitamin D, penicillin, gastro-protective agents) was started. Localised, firm puffiness at right submandibular region developed in the 1st week of the treatment (Fig. 1), while no steroid answer developed and proteinuria continued. Mumps and other infectious/non-infectious agents were excluded with clinical and laboratory findings. We determined that the peau d'orange appearance of the skin appeared in the second week of beginning of lymphoedema. Linear hypoechoic striations and thickening of subcutaneous tissue were detected with neck ultrasound (US), which were accepted as localised lymphoedema findings (Fig. 2). Doppler US was performed to the right submandibular region. Increase in vascularisation of soft tissue could not be detected beside normal vascularisation of parotid gland (Fig. 3). Invasive lymphangiography was not performed as the diagnosis of lymphoedema was also supported with lymphatic scintigraphy. Lymphatic scintigraphy applied bilaterally to both parotid region with 1 mCi <sup>99m</sup>Tc-nanocolloid subcutaneous revealed significantly decreased and prolonged lymphatic flow on the left.

In the treatment of localised lymphoedema, repetitive human albumin transfusions in order to increase oncotic pressure of intravascular circulation in addition to local massage and position were performed. Lymphoedema of the patient reduced in 2 weeks' time with this therapy, but nephrotic syndrome treatment is continuing.

## Discussion

The normal function of the lymphatics is to return proteins, lipids and water from the interstitium to the intravascular space. Lymphoedema results from impaired lymphatic transport leading to the pathologic accumulation of protein-rich lymphatic fluid in the interstitium, most commonly in the extremities.<sup>1</sup> Lymphoedema may be classified as primary

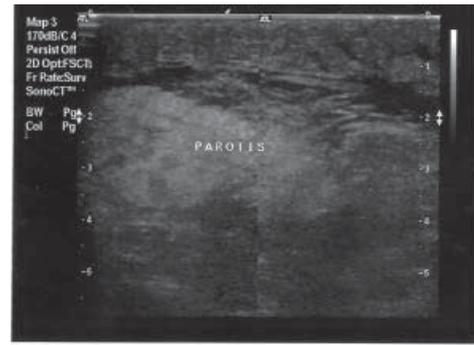


Fig. 2. Linear hypoechoic striations observed at right submandibular region with US (white arrow).

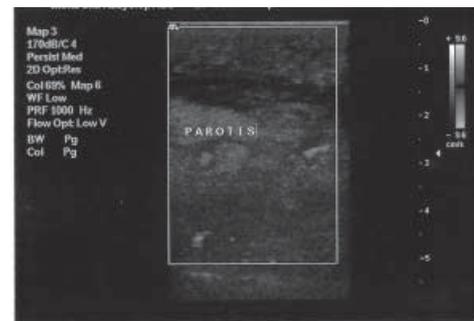


Fig. 3. Normal vascularisation of parotid gland without increase in vascularisation of soft tissue.

or secondary, based on underlying aetiology. Primary lymphoedema, which is further subdivided into 3 forms, including congenital lymphoedema, lymphoedema praecox, and lymphoedema tarda, depending on age at presentation, represents a developmental abnormality of the lymphatic system. These conditions are most often sporadic, with no family history, and involve the lower extremity almost exclusively. All 3 forms of primary lymphoedema originate most likely from a developmental abnormality that is present, but not always clinically evident, at birth. Some cases may become evident later in life when a triggering event or worsening of the condition causes the lymphatic transport capacity to exceed the volume of interstitial fluid formation, causing the patient to be unable to maintain normal lymphatic flow.<sup>2-4</sup> Secondary lymphoedema represents an acquired dysfunction of otherwise normal lymphatics. Secondary lymphoedema has an identifiable cause that destroys or renders inadequate otherwise normal lymphatics. It commonly results from damage or removal of regional lymph nodes through surgery, radiation, infection, or tumour invasion or compression.<sup>2,3,5</sup> We believe our patient had primary lymphoedema which was not clinically evident at birth or afterwards, until a triggering event, in this particular case the nephrotic syndrome, has developed.

High hydrostatic pressures in arterial capillaries force proteinaceous fluid into the interstitium, resulting in increased interstitial oncotic pressure that draws in

additional water. About 90% of the fluid returns to the circulation via entry into venous capillaries. The remaining 10% is composed of high molecular weight proteins and their oncologically associated water, flow into the lymphatic capillaries.<sup>5</sup> In a diseased state, the lymphatic transport capacity is reduced. This high oncotic pressure in the interstitium favours the accumulation of additional water. In this case, low oncotic pressure in intravascular circulation due to hypoalbuminemia caused a decrease in return of fluid from interstitial space to circulation.

Although infrequently required to establish the diagnosis, certain tests may be useful to confirm the diagnosis, to determine residual lymphatic function, to establish treatment preferences, and to evaluate therapy. Lymphangiography was the gold standard for evaluating the lymphatic system for many years, but as it has been shown to cause an inflammatory reaction of the endothelium of the lymphatic channels, leading to scarring, atrophy, and even luminal obliteration, it has been replaced by less invasive techniques such as lymphoscintigraphy. It can be used to define anatomy and patency, evaluate dynamics of flow and reversal of flow, and determine the severity of obstruction. An indication for CT scan or MRI is suspicion of malignancy, for which these tests offer the most information. Doppler ultrasonography is also used by some to evaluate flow in the lymphatic and venous systems.<sup>2</sup> The diagnosis of lymphoedema in our case was established with clinical findings, supported with US, Doppler US and scintigraphy findings. No further evaluation was performed to avoid invasive procedures.

In this particular case, lymphoedema developed at an unusual localisation, which has not been recorded before. The patient probably had congenital local hypoplasia of lymphatics in her neck region. After developing nephrotic syndrome, decreased oncotic pressure in circulation resulted in increased interstitial volume which on the one hand exceeded the capacity of lymphatic drainage and on the other hand caused the loss of patency of the lymphatic capillaries. This mechanism together with the gravity should result in lymphoedema in lower extremities. Wagner et al<sup>6</sup> reported a nephrotic syndrome case in a 6-year-old who developed lymphoedema in one leg 12 to 18 months after the appearance of nephrotic syndrome. However, it is not so in our case; lymphoedema was most prominent at the submandibular region.

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