Teaching Point  
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Histiocytosis X and renal insufficiency

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Introduction

Langerhans cell histiocytosis (LCH) is a rare disorder showing a wide spectrum of clinical manifestations ranging from single cutaneous lesions to multifocal systemic disease [1,2]. The typical infiltration consists of pathological monoclonal Langerhans cells together with lymphocytes, eosinophilic granulocytes and non-dendritic histiocytes [3]. Langerhans cells are antigen-presenting cells with features of dendritic cells, staining positive for CD1a [4]. One of their original functions is cutaneous immunosurveillance. LCH is rare and the incidence in adults is 1–2 cases per million, with a mean age of 35±14 years, and is slightly more prevalent in males [5,6]. Histological diagnosis is made if light microscopic morphological characteristics of the disease are found with positive staining for CD1α antigen [4,7]. In addition, Birbeck granules in the lesional cell that are detected with electron microscopy are also suggestive of the disease [4,7]. Typical manifestations of LCH in adults are central diabetes insipidus, bone, pulmonary, skin disease and dental involvement.

We report a case of a patient with progressive renal insufficiency due to multi-systemic manifestation of Langerhans cell histiocytosis including involvement of the kidneys. Treatment of LCH with chemotherapy resulted in stabilization of renal function.

Case

A 46-year-old male patient was admitted to our nephrology clinic in May 2006, with a 1-year history of impaired renal function with moderate proteinuria and glomerular erythrocyturia. In 1991, the patient was successfully treated for fibrous alveolitis with prednisolone. Two years later, the patient developed central diabetes insipidus. In 1999, Histiocytosis X (Langerhans cell histiocytosis, LCH) was diagnosed in a skin biopsy obtained from an axillary erythema (histological findings: cellular infiltration of the epidermis with histiocytes, co-expression of S100 and CD1a; negativity for lymphocytic markers and KL-1; positive PG-M1; epitheliotropism; highly-positive to MiB1). In the follow-up, he also developed bilaterally relapsing therapy-resistant external otitis and swollen cervical and submandibular lymph nodes. CT thorax revealed disseminated micronodular pulmonal opacities. Skeletal scintigraphy showed a suspicious focus in the proximal left tibia, and foci in the left mandible and left mastoid could be localized. Thin-layer magnetic resonance tomography of the sella turcica provided evidence for granuloma, with contrast enhancement in the area of the hypophyseal stalk. An intravenous prednisolone therapy with 100 mg was performed and the cutaneous focus showed a rapid diminution. Therefore, methylprednisolone (60 mg/day for 4 weeks) and vinblastine (7 mg/m² weekly) for 10 weeks (cumulative dose of 70 mg) was given, but had to be terminated due to emerging vinblastine-associated neuropathy. The therapy was switched to monthly pulses of methylprednisolone. In 2002, a further CT scan showed an enlargement of the right kidney with inhomogeneous parenchyma in both kidneys with multiple hypodense structures with a maximum diameter of 2 cm. No signs of renal obstruction were found. Because of the increasing impairment of renal function, the patient was admitted to our clinic in May 2006. In addition to the medical history outlined earlier, the patient reported oedema in his legs for many years, mild chills in the evening, no fever but sometimes night sweats. The previous chemotherapy was found to have no effect on the patient’s shortness of breath. Arterial hypertension had been found...
2 years before admittance (160/95 mmHg). He was on a daily medication of ramipril 10 mg, furosemide 20 mg, lercanidipin 10 mg, acetylsalicylic acid 100 mg and desmopressin nasal spray.

Upon admission, laboratory investigations (SI-units) showed a creatinine of 226 μmol/l (normal range 72–124 μmol/l), urea 15.4 mmol/l (normal range 1.7–8.3 mmol/l), potassium 4.96 mmol/l, C-reactive protein 112.8 mg/l (normal <5 mg/l), albumin 32 g/l, urate 522 μmol/l (normal 137–363 μmol/l), erythrocytes 3.2 Tpt/l (normal 4.5–5.9 Tpt/l), haemoglobin 5.5 Gpt/l (normal 8.7–10.9 Gpt/l), leucocytes 7.5 Gpt/l (normal 4.4–11.3 Gpt/l) and an erythrocyte sedimentation rate of 116/120 mm. Urinary analysis revealed a mild proteinuria (albumin 582 mg/g creatinine), but no haematuria and no leucocyturia. Serum concentration of complement factors C3 and C4 were normal and total complement (CH 50) was within normal limits. Immunoglobulins (IgG, IgM and IgA) were normal, and no autoantibodies were present (ANAs, ENAs, ANCAs and anti-ds DNA).

We performed a restaging because we assumed progression of the disease. The CT thorax showed a progress of pulmonary manifestation with fibrotic-cystic remodelling of the lungs. Cranial NMR showed no evidence for cerebral involvement. Iliac crest puncture histology showed a normocellular to hypocellular bone marrow with reduced haematopoiesis, middle grade left shift granulopoiesis, histiocytes were absent and staining for CD1a and S100 was negative. Due to the deterioration of renal function, we performed a renal biopsy. Light microscopy showed a severe destructive interstitial nephritis (Figure 1A–C). In the renal cortex, collagen-fibres, myofibroblasts, as well as infiltration by lymphocytes, monocytes/macrophages and plasma cells were found (Figure 1B and C). Furthermore, glomeruli with segmental adhesion of capillaries to the broadened Bowman’s capsule and a segmentally increased mesangial matrix were seen but basement membranes were of normal thickness (Figure 1D and E). Preglomerular arteries showed subendothelial fibrotic broadening. In the medulla, tubules and collecting ducts had enlarged basement membranes, and PAS-positive material was deposited intra-luminally. Immunohistochemistry did not reveal evidence for glomerular IgA, IgG and IgM. Glomerular C1q was absent but complement factor C3 was present in the preglomerular vessels, and fibrin was found within the interstitium and mesangium. In addition to the presence of CD8-positive T cells, many CD68-positive cells were found within the matrix-rich destroyed parenchyma, indicating infiltration with macrophages (Figure 2A–C). Interestingly, several CD1a-positive cells were found in the interstitium (Figure 2D and E). However, pathognomonic Birbeck’s granula were not found in the sample available for electron microscopy.

Due to progressive dyspnea and proven involvement of the lung, as well as the deterioration of renal function, the patient was classified as being at risk for
disease progression (group one, multi-system LCH and involvement of risk organs). Therefore, we started therapy with prednisolone and vinblastin [first prednisolone pulses: 500 mg/day over 3 days, then prednisolone 40 mg/m²/day orally for 4 weeks (day 1–28), then a dose reduction weekly over 2 weeks (Vinblastin 6 mg/m² weekly i.v. bolus for 6 weeks)]. Maintenance therapy for 1 year consisted of prednisolone 40 mg/m²/day orally for 5 days (day 1–5) and vinblastin 6 mg/m² on day one i.v. every third week. Currently, he receives 6-mercaptopurine 50 mg/m²/day.

In November 2006, the patient was readmitted for staging. He still reported neuropathic complaints and dyspnea with exertion, but renal function was stabilized and improved (creatinine 130 µmol/l, creatinine-clearance 54 ml/min), proteinuria slightly increased (albumin 973 mg/g creatinine). Pulmonary manifestations had not deteriorated in the follow-up CT, and a reduction of mediastinal lymph nodes and pulmonal infiltrations could be demonstrated. Skin lesions had improved significantly.

Discussion

LCH is a rare disorder, and is categorized as a class I histiocytosis syndrome. Mass lesions of dendritic cells are found as a single lesion but can also involve multiple sites as well as multiple organs as a diffuse disease. Extent of the disease at presentation as well as the involvement of ‘risk’ organs (liver, spleen, lung and bone marrow) affect prognosis and treatment. The disorder is typically found in children, even though recent studies have shown an approximate occurrence of 30% in adults with an incidence rate of 0.18/100,000 [5,7,8]. LCH can be found as a primarily isolated manifestation in the lungs, slightly more frequent in males than in females between 20 and 40 years of age, of whom most are smokers. Gender predominance may drift according to a changing pattern of smoking [9,10]. Our patient showed the first manifestation in the lungs, followed by involvement of multiple other organs a few years later. According to Ladisch et al. [11] LCH can be categorized as a multi system disease or single system disease. Patients with single system disease, in bone, skin or lymph node have a better prognosis. Multiple organ involvement has a higher mortality of 10–20%, compared with patients with only one organ involvement [12]. In our case, after histological verification of histiocytic infiltration of skin with typical staining (CD1a, S100), the diagnosis of Langerhans cell histiocytosis was confirmed. Sites of organ manifestation which are typical of LCH [lung, bone (e.g. mandible, ear), hypophysis, skin and lymph nodes] were present in our patient, but no evidence for an involvement of liver or the haematopoietic system was found. The kidneys appeared enlarged with inhomogeneous parenchyma. Irregular contrast enhancement was visible in the CT scans. Clinically, hypertension, oedema and mild proteinuria were present. Renal function was significantly impaired. Renal biopsy revealed severe destructive and scaring interstitial nephritis with many CD68 and a few CD1a—positive cells in the interstitium suggesting the possibility of a renal manifestation of the LCH.

Though renal involvement of LCH is uncommon, a case of LCH with membranous glomerulonephritis in a young man with bone manifestation has been previously reported [13]. In 2005, Anabi et al. [14] described a nephrotic syndrome caused by membranoproliferative glomerulonephritis in a 20-year-old

![Fig. 2. Immunohistochemistry. (A) Infiltration of T cells in the interstitium identified by staining for CD3 (magnification 200×). (B) Many of these T cells were CD8-positive (magnification 200×). (C) In addition, many CD68-positive cells were present in the interstitium (magnification 200X). (D, E) There were few Langerhans (CD1a-positive) cells infiltrating the interstitium (magnification D: 400, E: 1000).](https://academic.oup.com/ndt/article-abstract/22/12/3666/2588712)
female suffering from disseminated LCH. Moreover, minimal change nephropathy was described in a case of a 7-year-old boy with Rosai–Dorfman disease, a benign non-Langerhans histiocytosis of the lymphoid system (class II histiocytosis of mononuclear phagocytes other than Langerhans cells), which was resistant to prednisolone, but responded to oral cyclophosphamide treatment [15]. In all these publications, a histological confirmation of renal infiltration by LCH was not presented. In contrast, previously reported cases with renal involvement in Rosai–Dorfman disease described acute renal failure due to the renal parenchymal infiltration by lymphoplasmocytic cells or histiocytes and renal amyloidosis [16–18]. Harik and Nassar recently presented a case of extranodal Rosai–Dorfman disease with infiltration of the kidney [19]. It was observed that in contrast to Langerhans histiocytes, Rosai-Dorfman histiocytes did not stain positive for CD1. The only case of a documented infiltration of kidney by LCH is reported by Goyal et al. [20]. An 18-month-old male with a presumptive diagnosis of LCH (cytology from swollen lymph node) died 10 months after chemotherapy. In the autopsy, LCH infiltration had been seen in the liver, pancreas and kidneys [20]. Volmer reported on a case of LCH with infiltration of the kidneys with plasma cells and a compact granulation tissue interspersed with infiltrations of histiocytes, but immunohistochemistry was not performed [21].

In conclusion, we report on a patient with severe multi-system LCH, developing interstitial nephritis and renal insufficiency. The histology of the renal biopsy showed infiltration with CD1a-positive cells. Although there were only a few CD1a-positive cells and the majority of the interstitial infiltrate were T cells and CD68-positive cells, the severe interstitial nephritis is very likely an extranodal manifestation of LCH. Renal involvement in this disease is rare. To the best of our knowledge, this is the first report showing that chemotherapeutic treatment of LCH with prednisolone and vinblastine was able to improve renal function in LCH with renal involvement.

Teaching points

- Renal involvement is rare in Langerhans cell histiocytosis
- Interstitial nephritis due to infiltrating histiocytes and other immune cells may point to organ manifestation of this systemic disease
- There are different types of histiocytes, not all bearing the same markers (e.g. CD1a)
- Chemotherapy for generalized histiocytosis can stabilize renal function, presumably due to improvement of interstitial nephritis

Conflict of interest statement. None declared.

References


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