Case Report

Disseminated cutaneous plasmacellular granuloma associated with membranous glomerulonephritis

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Introduction

Plasmacellular granuloma (PG), also called inflammatory pseudotumour, is a rare benign inflammatory disease characterized by granulomatous proliferation of plasma cells, lymphocytes, eosinophils and neutrophils; it has been described as an isolated tumour occurring in solid organs, e.g. lung, spleen, liver, and in other more infrequent locations [1,2]. A cutaneous PG has been observed in five cases [3,4]; in all patients described, the tumour was unilocular and could be removed by surgical excision without clinical sequelae.

We describe a case of a child with disseminated cutaneous PG associated with membranous glomerulonephritis. The disseminated cutaneous tumours and the nephrotic syndrome responded to treatment with oral prednisone; however, the child experienced several relapses of the cutaneous lesions until maintenance therapy with prednisone and mycophenolate mofetil (MMF) was introduced.

Case

A 4.5-year-old Turkish boy developed a palpable pea-sized tumour in the right cheek; this was initially diagnosed as an enlarged lymph node or a small abscess. Within half a year, disseminated subcutaneous brownish indolent tumours (up to 1 cm in diameter) were observed mainly on both upper legs and in the lower trunk region. A skin biopsy from the left femoral region was performed about 10 months after the initial swelling of the cheek and showed PG (Figure 1).

Since PG is considered a benign lesion with reported examples of a self-limiting course [5], no specific medical therapy was initiated. However, a slow progression of the cutaneous lesions was observed and after 3 months the child was referred to our institution because of generalized oedema and proteinuria.

On admission, weight was 18 kg, height was 103 cm, body temperature was 36.5°C and blood pressure was 100/60 mmHg. Physical examination was remarkable for generalized oedema with ascites and disseminated cutaneous tumours resembling cutaneous lymphoma (Figure 2). The abdominal ultrasound showed enlarged hyperechogenic kidneys.

Laboratory investigations showed signs of the nephrotic syndrome (total protein 4.1 g/l, albumin 2.3 g/l, cholesterol 607 mg/dl, triglycerides 611 mg/dl, urinary protein 7.2 g/d) as well as hypergammaglobulinaemia (IgG 14.3 g/l, IgA 5.5 g/l, IgM 1.17 g/l). The WBC was 18 200 with 50% segmented granulocytes, 41% lymphocytes, 6% monocytes; haemoglobin was 12.9 g/dl. T-cell subsets were normally distributed and lambda and kappa light chains were not detected in serum, but in high concentrations in urine (Bence–Jones protein positive).

Serological studies for viral infections showed antibodies against EBV which were compatible with a historical infection (EBV-VCA IgG 1:256, EBV-VCA IgA negative, EBV EA IgG 1:64, EBNA 1 Ab 1:128, EBNA 2a Ab1:128, EBNA 2b Ab 1:128). The PCR for EBV was negative both in serum and by in situ hybridization performed in the skin biopsy material (Prof. Dr Müller-Lantzsch, Homburg, Germany). The patient had antibodies against RS-virus (1:80) and against measles, but not against hepatitis A, B and C, coxsackie B, influenza, herpes simplex and varicella.

A kidney biopsy revealed membranous glomerulonephritis stage II (Figure 3 a and b). A repeat skin biopsy taken from the left femoral region (to rule out lymphoma) confirmed the diagnosis PG. Immunohistochemistry showed inflammatory changes with the presence of monocytes, macrophages and histiocytes, B cells, and plasma cells expressing lambda and kappa light chains, but no evidence of monoclonal gammopathy or malignant cell growth.
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Fig. 1. Plasmacellular granuloma on first skin biopsy taken from a cutaneous lesion on the right upper leg.

Fig. 2. Appearance of the legs on initial physical examination.

Fig. 3. (A) Kidney biopsy performed about 14 months after occurrence of primary lesion of PG. On light microscopy there is enlargement of the glomerular basement membrane, and some tubular atrophy and interstitial fibrosis. (B) Kidney biopsy, immunofluorescence staining reveals the characteristic findings of membranous glomerulonephritis: generalized granular subepithelial deposits of IgG and C3d along the glomerular basement membrane, to a lesser extent deposits of IgA and IgM.

After therapy with aciclovir (because of the reported association of PG with EBV) for 10 days and intravenous high-dose IgG (given over 2 weeks) had shown no effect, steroid therapy was started with oral prednisone 2 mg/kg/day.

The further clinical course was rather stormy and characterized by generalized oedema with severe ascites formation, which was initially unresponsive to medication with albumin, furosemide and ACE-inhibitors (captopril). The child developed arterial hypertension, focal seizures, acute pancreatitis and Steven–Johnson’s syndrome which was believed to be secondary to medication with any one of the following or the combination thereof: carbamazepine, phenytoine, captopril, vancomycin, furosemide.

The child recovered from all these complications and after about 3 months of steroid treatment, proteinuria rapidly diminished. The disseminated cutaneous lesions completely disappeared within the next months. However, a palpable buccal tumour, smaller than the original primary lesion, persisted. Prednisone was discontinued after 8 months. The child remained free of proteinuria and the ultrasound of the kidneys showed normalization of hyperechogenicity, but persisting enlargement of both kidneys. A repeat kidney biopsy after 12 months revealed persistence of the lesions of membranous glomerulonephritis (stage II).

Ten months later, the tumour in the cheek showed noticeable enlargement on palpation and on ultrasound. Prednisone was again started at 2 mg/kg/day.
and tapered over 6 months, resulting in shrinkage, but not disappearance of the lesion. When enlargement was again documented by ultrasound 2 months after discontinuation of prednisone, surgical excision was performed (Figure 4). Histology again confirmed PG.

The child remained free of symptoms for 8 months, but then experienced a relapse with multiple palpable subcutaneous tumours on both upper legs; these lesions could be readily demonstrated by ultrasound and magnetic resonance imaging (Figure 5). Maintenance immunosuppression with MMF was started at a dose of 500 mg b.i.d., but had no effect. Although no further increase of these lesions was noticed, prednisone therapy (2 mg/kg/day) had to be resumed at the request of the parents after 3 months. Again, rapid regression of lesions was observed and under continuation of MMF alone, remission persisted for 6 months. After another relapse, maintenance therapy with prednisone (5 mg q.o.d.) and MMF (25 mg/kg q.d.) has kept the patient in remission for a total of 8 months. The child has proceeded to grow along the third percentile and his weight is currently at the 50th percentile for Turkish children. Physical and mental development is otherwise normal for age.

Discussion

There have been five previous reports of cutaneous PG, all were described in adults [3,4]. In all instances, the tumour was solitary and could be removed without complications. To our knowledge, the present case is the first report of a disseminated form of PG. Moreover, this rare disease occurred in a young child, was associated with membranous glomerulonephritis, and characterized by a relapsing steroid sensitive clinical course. To our knowledge, the only previously reported association of PG with renal disease is the occurrence of renal amyloidosis with nephrotic syndrome in a patient with a large intra-abdominal PG [6].

From a morphological point of view, the differential diagnosis of multiple cutaneous tumours includes Kaposi sarcoma, nodular fasciitis, cutaneous lymphoma, histiocytosis with lymphadenopathy (Rosai-Dorfman disease) and Kimura’s disease [1,3,7].

Membranous glomerulonephritis, characterized by subepithelial immune complex deposition along the glomerular basement membrane, is typically generated by persisting antibody production in the presence of excess antigen, resulting in formation of soluble circulating immune complexes. Known primary diseases include chronic infections (malaria, syphilis), persisting viral infections (hepatitis B, C) and malignant tumours, especially of the lymphatic system [8]. We speculate that in the present case, immunoglobulin production (as evidenced by hypergammaglobulinemia) by plasma cells of the disseminated PG was responsible for the glomerulonephritis. We have no explanation for the persistence of membranous lesions after the disappearance of proteinuria; it is possible that the histological alterations may take more time to resolve.

Cutaneous lesions associated with membranous glomerulonephritis are rare, but have been occasionally observed in angioimmunoblastic lymphadenopathy (giant lymph node hyperplasia, Castelman’s syndrome [8]), Kimura’s disease [9] and persisting EBV infection [3,8]. In our case, histology could establish the diagnosis of PG and in situ hybridization for EBV was negative. Since the history of the patient and serological studies were also negative, we have no explanation for the occurrence of PG which has been reported to occur secondary to infectious stimuli [1].

It seems remarkable that the disseminated cutaneous lesions were responsive to steroid therapy as described for solitary extracutaneous lesions [5]; however, our case illustrates the apparent possibility of recurrence of PG. We have therefore chosen to explore treatment with MMF, which has antiproliferative effects on T and B lymphocytes and anti-tumour activity and has been used with success in other skin diseases [10]. Monotherapy with MMF did not achieve a remission, but seemed to prevent further spread of the lesions. In the present case, a combination therapy with low-dose prednisone and MMF resulted in a sustained remission.

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References


Fig. 5. Magnetic resonance imaging of the legs showing disseminated nodular cutaneous lesions.

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