Idiopathic Plasmacytic Lymphadenopathy with Polyclonal Hypergammaglobulinemia Accompanied with Cutaneous Involvement and Renal Dysfunction

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Idiopathic plasmacytic lymphadenopathy (IPL) with polyclonal hypergammaglobulinemia has been proposed as a new disease entity resembling the plasma cell type of multicentric Castleman’s disease. Here, we report a case of IPL accompanied by renal failure and skin involvement. A 35-year-old man was admitted for advanced renal failure, anemia, systemic lymphadenopathy and skin rashes. Laboratory examinations indicated polyclonal hypergammaglobulinemia and elevated serum interleukin-6 (IL-6). Biopsy of a cervical lymph node revealed follicular hyperplasia with normal germinal centers, sheets of polyclonal proliferating plasma cells and the absence of marked proliferation of blood vessels in the interfollicular area. Lesions of the kidney and skin also had pathological characteristics of IPL. Following a diagnosis of IPL, corticosteroid therapy successfully improved the anemia and hypergammaglobulinemia, and serum IL-6 levels decreased to a normal range. This case may give suggestions about diagnosing and preventing the progression of complications from this disease entity.

Key words: IPL — renal failure — skin involvement — corticosteroid therapy

INTRODUCTION

Idiopathic plasmacytic lymphadenopathy (IPL) with polyclonal hypergammaglobulinemia was first described by Mori et al. (1) as a new disease entity resembling the plasma cell type of multicentric Castleman’s disease (MCD) in the early 1980s. Although some of the clinical findings of IPL are similar to those of MCD including multicentric lymphadenopathy, prominent polyclonal hypergammaglobulinemia, elevated serum interleukin-6 (IL-6) levels and anemia (2–4), IPL appears to demonstrate clinicopathologic features that differ from those of MCD in some respects (1,5). Whereas MCD exhibits an aggressive and usually fatal course associated with infectious complications or malignant tumors like Kaposi’s sarcoma and B-cell lymphoma in one-third of patients, IPL was reported to have a less aggressive or sometimes self-limiting clinical course (1). The histological findings of IPL differ from MCD in some respects: (i) the lymphoid follicles of IPL usually have normal or hyperplastic germinal centers, whereas those of MCD have atrophic hyaline vascular germinal centers; (ii) in IPL, there is no interfollicular vascular proliferation, which is a characteristic histological finding of MCD; (iii) the number of CD57-positive germinal center T-cells is lower in MCD than in IPL; (iv) the follicular dendritic cell (FDC) network in the lymphoid follicles usually show a normal/reactive pattern in IPL, whereas the majority of lymphoid follicles show abnormal ‘tight/concentric’ or expanded/disrupted FDC networks in MCD (3,5). Organ involvement in IPL is not common (5) and reports of IPL with pathologically confirmed involvement of skin and kidney are rare.

Here, we report an IPL case with long-standing skin eruptions and advanced renal failure due to infiltration of IPL that were both pathologically confirmed.

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CASE REPORT

A 35-year-old man was admitted to our hospital for the examination of advanced renal failure and anemia, which had been pointed out in his annual health checkup for the preceding several years. He felt generally well and had no episodes of fever, dyspnea or edema in the extremities. He complained of slight fatigue, palpitation and weight loss of 7 kg over the previous year. There was nothing notable in his family history or past history other than brown rashes on his face and trunk that had remained unchanged for the last 15 years.

Physical examination on admission demonstrated anemia of the conjunctivae and skin. Brown rashes were scattered on the face, upper abdomen and back. Multiple lymph nodes were enlarged on both sides of the neck, axillae and groin, and were from 0.5 to 1.5 cm in diameter, elastic firm, movable and unpainful. The chest examination was normal, and the liver and spleen were not palpable. No edema in the extremities or neurological abnormalities were observed.

The patient’s hemoglobin level was 6.3 g/dl; white blood cell count, 7.1 \times 10^3/mm^3; and platelet count, 27.6 \times 10^3/mm^3. His total serum protein value was 9.5 g/dl (albumin, 27.6% and globulin, 51.4%), and serum protein electrophoresis revealed a polyclonal pattern. Measurement of serum immunoglobulin (Ig) levels revealed the following values: IgG, 4556 mg/dl; IgA, 540 mg/dl; IgM, 162 mg/dl; IgD, 8.5 mg/dl; and IgE, 4832 mg/dl; serum IgG4 level accounted for <5% of the total IgG. Urinalysis indicated poteinuria and hematuria; no Bence-Jones protein was detected in the urine. The biochemical and serological tests revealed elevated values of lactate dehydrogenase (LDH) (331 IU/l), blood urea nitrogen (89 mg/dl), creatinine (6.5 mg/dl) and C-reactive protein (CRP) (4.66 mg/dl). IL-6 was markedly elevated, 27 pg/ml, and soluble IL-2 receptor was 1757 U/ml. Collagen, autoimmune, endocrine or infectious diseases were excluded by the laboratory data and clinical findings. The bone marrow plasma cells were normal in number (0.8%) and morphology. Computed tomographic (CT) scanning of the whole body showed only enlargement of the superficial lymph nodes. Normal/reactive pattern. There were only few plasma cells positive for IgG4 or human herpes virus 8 detected in the lymph node or skin lesions.

On the basis of the clinical and pathological features, a diagnosis of IPL with polyclonal hypergammaglobulinemia was made. On admission, dialysis was started for the advanced renal failure, and 3000 U of erythropoietin twice a week was subcutaneously administered. However, the anemia did not improve. The patient was treated with 1000 mg of methylprednisolone for 3 days followed by 1 mg/kg body weight of oral prednisolone for 4 weeks, which was thereafter tapered by 5 mg a week. The anemia gradually improved, serum IL-6 decreased to undetectable levels and serum IgG also decreased (Fig. 2). Systemic lymphadenopathy also disappeared after the administration of corticosteroid. In contrast, renal dysfunction and skin rashes persisted despite the treatment. The adverse effects of corticosteroid treatment were mild hyperglycemia and herpes zoster. Although the patient required maintenance dialysis, he was discharged after the improvement of his general symptoms, and remained asymptomatic for 18 months with 5–15 mg/day of prednisolone as a maintenance therapy.

DISCUSSION

Our patient fulfilled the clinical diagnostic criteria of IPL including less-aggressive clinical course and laboratory data, and the overall pathological findings were consistent with IPL rather than MCD. Other differential diagnoses such as collagen, autoimmune and infectious diseases, and POEMS syndrome were ruled out. Malignant lymphoma or other malignancies were undetectable by CT scan and 67Ga-citrate scintigraphy and pathological findings. IgG4-related disease was a recently proposed disease entity associated with autoimmune pancreatitis and other disorders characterized by elevated serum IgG4 levels and the infiltration of IgG4-positive plasma cells into the affected tissue, including lymph nodes (6–10). Although the features of IgG4-related lymphadenopathy sometimes mimic MCD or malignant lymphoma, this case was ruled out by low serum level of IgG4 and lack of infiltration of IgG4-positive plasma cells into the affected organs by immunohistochemical study. Other data such as elevated level of IL-6, LDH and CRP were also inconsistent with IgG4-related disorders.

This case was particularly notable for the complications of renal failure and long-standing skin rashes. In five reported cases of IPL with skin involvement, the rashes had appeared 3–20 years prior to the diagnosis (5,11,12). In this case, the skin lesions showed lymphoplasmacytic infiltration around the small vessels in the papillary dermis, a common pathological finding of IPL. It is possible that such skin manifestations are
the initial sign of IPL. Sixteen cases of IPL were reported to have renal involvement with various degrees of proteinuria, hematuria and renal failure (5,12–15). Although most of them had mild to moderate renal dysfunction, hemodialysis was needed in only two cases. The main histological features of renal involvement in IPL are mesangial proliferation and/or plasma cell infiltration into the interstitial space. It is supposed that overproduction of IL-6 by unknown etiology in IPL induces proliferation of mesangial cells and infiltration of plasma cells into the renal interstitium, and these processes may be augmented by paracrine or autocrine of IL-6 by primed mesangial cells and infiltrating plasma cells (16,17). These mechanisms may be important keys to the renal damage and disease symptoms of IPL; however, much remains to be

Figure 1. (a) Lymph node: sheets of proliferating mature plasma cells in the interfollicular area were observed. (b) Renal tissue: on high-power field, multifocal plasma cell infiltration in the interstitium was noted. (c) Skin: a skin specimen contained lymphoplasmacytic infiltration around the small vessels in the papillary dermis. (d and e) Immunoperoxidase studies of lymph node. Plasmacytes demonstrated a polyclonal pattern by kappa (d) and lambda (e) stainings. A color version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org.

Figure 2. Clinical course. Levels of hemoglobin, IL-6 and IgG are shown before and after the corticosteroid treatment.
discovered. Since the renal damage in our case resulted from glomerulosclerosis due to multifocal infiltration of plasma cells into the interstitium, it was reasonable that the renal failure was refractory to corticosteroid therapy despite successful reduction of IL-6 and IgG. Although advanced renal failure is rare in IPL, it should be noted that renal function may progressively decline in IPL patients and strategies should be taken to prevent renal failure prior to the advanced stage.

The treatment of IPL has not yet been established. Some reports have indicated the efficacy of corticosteroid treatment or anti-cancer chemotherapy (5,11,12). In the present case, we chose corticosteroid treatment as the first-line therapy because various clinical manifestations of IPL are thought to be caused by overproduction of IL-6 (5,14,18). Corticosteroid inhibits the release of pro-inflammatory cytokines, such as IL-6, from macrophages and T- and B-lymphocytes, and was actually effective in our patient in terms of the reduction of IL-6 and IgG and improvement of anemia and fatigue. Tocilizumab, a humanized anti-human IL-6 receptor antibody, may also improve the symptoms of IPL (19).

In conclusion, we report a case of IPL with advanced renal failure and long-standing skin manifestation showing infiltration of polyclonal plasma cells. Corticosteroid treatment was effective in controlling IL-6 concentration and anemia, and the patient has remained asymptomatic for 18 months. More information and experience of similar cases are required to clarify the clinicopathologic features of IPL and to establish the optimal treatment.

Conflict of interest statement

None declared.

References