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Sino-Pulmonary-Renal disease in a child

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CASE REPORT

A 7-year-old girl was admitted to our unit with a 1-year history of nonpruritic rash and recurrent sinusitis. Past history revealed that she had been operated for aortic coarction and patent ductus arteriosus when 40 days old. Family history was unremarkable. On physical examination, she was short (3-10 percentile) and had a low-set hairline, hepatosplenomegaly and a maculopapular erythematous rash on the face, trunk and limbs.

Laboratory examinations revealed a normal blood count, erythrocyte sedimentation rate, serum C-reactive protein and increased liver enzymes with an ALT and AST of 167 and 256 IU/ml, respectively. She had normal immunoglobulin, complement and angiotensin converting enzyme levels. Antinuclear antibody, anti-dsDNA, extractable nuclear antigens, antineutrophil

cytoplasmic antibodies (ANCA), antimyeloperoxidase and antiproteinase III (PR3), hepatitis B and C serology were negative. Urinalysis was normal. Her peripheral blood chromosome analysis was consistent with mosaic Turner syndrome (45,X/46,XX, del X p). Skin biopsy revealed leukocytoclastic vasculitis. Over the next 2 months, she developed dyspnea and hoarseness. An infectious cause was not

found. Upper respiratory tract examination showed features of chronic sinusitis. Chest radiograph revealed subglottic stenosis, bilateral diffuse interstitial infiltrations and atelectasis. Oral prednisolone (0.5 mg/kg/day) and methotrexate was started for a preliminary diagnosis of pulmonary vasculitis. However, she did not respond. Flexible brochoscopy was planned to obtain a biopsy but was not completed due to severe epistaxis.

Subsequently, she developed proteinuria and hematuria. A repeated indirect immunofluorescence test for ANCA was positive with c-ANCA pattern, although PR3 antibodies were negative by ELISA. The family refused renal biopsy.

Although tissue diagnosis was not available, Wegener's granulomatosis (WG) was considered as the probable diagnosis. Cyclophosphamide (1mg/kg/day, p.o.) was added to the oral steroid treatment. The following year was characterized by frequently intervening severe respiratory tract infections despite trimethoprim/sulphamethoxazole prophylaxis. Immunosuppressive treatment was frequently put off because of these infections and she was hospitalized several times due to persistent and recurrent pulmonary inflammation. The chest radiograph suggested pulmonary vasculitis or infection and she was treated with pulse methylprednisolone, intravenous antibiotic and antifungal agents multiple times (Figure 1).

Renal biopsy was performed one year later and revealed focal cresentric, diffuse segmental and necrotizing ''pauci-immune'' type glomerulonephritis. Immunofluorescence studies showed no immune complex deposition. Direct laringoscopic examination of the vocal cords showed granulomatous lesions. Biopsy revealed necrotic material, inflammatory cells and gram positive cocci. Wegener's granulomatosis was diagnosed according to American College of Rheumatology criteria with recurrent sinusitis and upper respiratory tract findings (epistaxis, subglottic stenosis, granulomatous lesions on vocal cords) and pulmonary involvement with chest radiographs showing fixed infiltrates, hematuria and renal biopsy findings [1].

She was plasmapheresed three times a week and cyclophosphamide was started again when her white blood count (WBC) was above 4000/mm^3. At follow-up, she developed subcutaneous nodules on the face, trunk and extremities (Figure 2). One of these nodules was biopsied and a diagnosis was established.

DISCUSSION

Pulmonary vascular inflammation can be seen in a variety of primary lung diseases and in the setting of numerous systemic illnesses. Pulmonary vasculitis may be a central feature of the pathologic process as in WG, Churg-Strauss syndrome,

microscopic polyangiitis and lymphomatoid granulomatosis. Henoch-Schoenlein purpura, Behçet's disease, giant cell arteritis, Takayasu's disease, leukocytoclastic vasculitis and cryoglobulinemia may also have a pulmonary involvement, but quite rarely [2-4].

The presented patient had recurrent and persistent inflammation in the upper and lower respiratory tracts, renal biopsy verifying necrotizing pauci-immune type glomerulonephritis and positive serology for c-ANCA. The clinical course very similar to WG. The clinical presentation fulfilled the diagnostic criteria for WG. She had upper respiratory tract involvement with severe epistaxis, recurrent sinusitis and subglottic stenosis. Leukocytoclastic vasculitis, segmental and pauci-immune type glomerulonephritis, positive serology for c-ANCA, recurrent and persistent pulmonary inflammation and chest radiographs showing diffuse interstitial infiltrates were all suggestive of WG [1,2,5]. On the other hand, polyarteritis nodosa may present with similar renal features; however, the upper respiratory tract involvement, and the pattern of ANCA was incompatible. Her lung involvement was never in the form of asthma and she had no eosinophilia. Anti-glomerular basement-antibodies were negative. She had no features suggesting HSP, Behçet's and Takayasu's during her long follow-up.

Thus, her clinical diagnosis was a probable WG although we had not shown the granulomatous lesions in her biopsies and failed to show a high PR-3 ANCA titer. However, the final biopsy from the nodules revealed a new diagnosis.

FINAL DIAGNOSIS

Light microscopic examination of the skin biopsy showed a nodular lesion in subcutaneous fat tissue. In this lesion, angiocentric and angiodestructive proliferation of lymphohistiocytic cells principally involving small and medium sized vessels were observed. The infiltrate was composed of various mononuclear elements including lymphocytes, plasma cells and macrophages, with foci of bizzare lymphohistiocytic cells demonstrating much pleomorfism and increased number of mitotic figures. Immunohistochemically, most of lymphoid cells expressed CD3, and some of them expressed CD8. Between these cells, there were CD68 positive histiocytes.

These histopathologic findings were consistent with grade II angiocentric immunoproliferative lesion, that is, lymphoid granulomatosis (LYG).
Our patient had a multisystemic process, with clinical evidence of upper respiratory tract, pulmonary, hepatic, cutaneous, renal and probable spleen involvement consistent LYG.

LYG is a rare angiocentric and angiodestructive lymphoproliferative disorder with prominent pulmonary involvement [2,6]. It was initially described by Liebow *et*

al. as a necrotizing pulmonary vasculitis that may progress to lymphoma [6]. Skin, central nervous system and kidneys are affected in one-third of the patients. Involvement of the upper airways, eyes, liver, spleen, adrenal glands, pancreas, gastrointestinal tract, heart and lymph nodes have also been documented [2,6-8]. The clinical course may vary from spontaneous regression, resolution with treatment or progression to lymphoma.

LYG is very rare in childhood [6, 8, 9-11, 12-16]. In Liebow's original series with 40 patients, only one patient was a child and in Katzenstein's series with 152 patients, 12 patients were under the age of 20 [6,8]. The clinical signs are extraordinarily diverse, and the radiologic and laboratory findings are nonspecific. Therefore, the diagnosis of LYG is usually missed or delayed. The etiology of LYG is unknown. Recent studies have indicated that it is an Epstein-Barr virus associated B cell lymphoproliferative disorder with a background of reactive T lymphocytes [10, 17-19]. Immunodeficiency, Epstein-Barr virus, genetic and familial factors have been proposed in the pathogenesis [6-8,13, 15, 18-21]. There are no specific laboratory findings in LYG.

Upper respiratory tract involvement is a cardinal feature of WG, nearly reported in 92% of the patients although rarely observed in LYG [1,2,5,6]. Pulmonary involvement has been described in all patients with WG and LYG [1,2,5,6,8]. Massive destruction of lung parenchyma leading to respiratory insufficiency represented the major cause of death in LYG [6,8,15]. Radiologic findings are not specific to help in differential diagnosis. Multiple bilateral nodular infiltrates are present in 80% of cases in both WG and LYG [2,22]. Cavitation can be observed in 20 to 30% of cases in both diseases. Diffuse interstitial infiltrates are the second most frequent radiologic finding, present in 45% of the patients with LYG [22].

Renal involvement has been described in 80% of the patients with WG and one-third of the patients with LYG [1,2,5,6,8,15]. However clinically evident renal disease like in our case has rarely been reported in LYG [15]. In Liebow's initial series, 45% of the cases showed nodular lesions with atypical lymphoreticular infiltrates with necrosis and vasculitis [6]. A segmental necrotizing pauci-immune type glomerulonephritis is a feature of WG, while glomerular involvement is strikingly absent in LYG [6,8,15]. Hepatomegaly was reported in 12% of Katzenstein's series and carried a worse prognosis [8].

Skin involvement has been reported equally as 46% in both WG and LYG [5,15]. These lesions included palpable purpura, ulcers, vesicles, papules and subcutaneous nodules in WG and erythematous, macular or plaque-like lesions and rarely subcutaneous nodules in LYG. Biopsy is important for early diagnosis when

cutaneous involvement is present, however our patient developed subcutaneous nodules late in the course.

Liebow *et al.* considered LYG as a distinct and separate disease entity although several features histologically resembled WG [6]. A destructive inflammatory vasculitis is a feature of both LYG and WG, however the composition of the infiltrate differs. An atypical infiltrate with lymphoreticular cells with plasmocytoid features predominating over mature lymphocytes and plasma cells, rare polymorphonuclear leukocytes (PMNL's) or eosinophils and intense proliferative activity are characteristic features of LYG. The infiltrate in WG is composed chiefly of PMNL's, histiocytes and occasional eosinophils with a relative sparse population of lymphocytes and plasma cells [6,8,15,20,23].

An optimal treatment protocol has not been established for LYG yet and is somewhat similar to WG. Immunosuppressive drugs and combined chemotherapy (cyclophosphamide, corticosteroids and vincristine) have been applied [6-9,10,20]. After the diagnosis was established, we have started chemotherapy for the presented patient. Unfortunately, she died during chemotherapy due to pulmonary hemorrhage.

Surgery and radiotherapy have been used as an adjunctive therapy [7,8,16,23]. Fauci *et al.* reported remissions lasting 5 years or more in approximately half of their 15 patients and concluded that early diagnosis and prompt treatment could establish a good prognosis [7]. Koss *et al*. reported no significant difference in outcome of patients treated with corticosteroids, chemotherapy and radiation [23]. Interferon-alpha 2b, which has antiviral, antiproliferative and immunomodulatory effects, has been proposed as a new treatment modality and achieved some favorable results [13,19].

CONCLUSION

Our case strongly emphasizes the clinical similarities of WG and LYG and reveals the diagnostic challenge and delay in patients with LYG. LYG should be considered in the differential diagnosis of pulmonary vasculitis and mutisystemic clinical findings, albeit very rare in the pediatric age group. As there are no specific clinical, laboratory and radiologic findings for LYG, a definite diagnosis may only be possible by histopathologic examination. Though it is often considered as a fatal vasculitis without an evident response to treatment, early recognition and treatment may prevent progression into a lymphoma.

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