Increased Interleukin-6 (IL-6) Production in a Young Child with Clinical and Pathologic Features of Multicentric Castleman's Disease

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A 21-month-old boy presented with a papular rash, lymphadenopathy, and splenomegaly. He developed symmetric polyarthritis, fever, and progressive glomerulonephritis. Serologies for viral agents including HIV were negative. Antinuclear antibody was transiently positive, but no anti-DNA antibodies were present. CH50 and serum C3 values were low. Biopsies of skin, kidney, bone marrow, and lymph node were obtained. There was a perivascular and periadnexal lymphocytic infiltrate in the skin, with a normal epidermis. Renal biopsy showed proliferative mesangial glomerulonephritis. Bone marrow showed an increased number of plasma cells. Lymph node showed histologic changes described in multicentric Castleman's disease including marked follicular hyperplasia, vascular proliferation, and interfollicular expansion with numerous plasma cells. IL-6 mRNA was demonstrated in cells in the marginal zone and interfollicular regions of the node by *in situ* hybridization. Likewise, the serum IL-6 level was elevated during a clinical exacerbation of the patient's nephritis. These data suggest an underlying lymphoproliferative disorder, such as Castleman's disease, with overproduction of IL-6 resulting in systemic features of the disease, including glomerulonephritis.

KEY WORDS: Castleman's disease; angiofollicular lymphoid hyperplasia; autoimmunity; glomerulonephritis; interleukin-6.

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INTRODUCTION

Castleman's disease is a form of lymphadenopathy characterized by follicular hyperplasia, vascular proliferation, and various degrees of plasmacytosis. In 1956, Castleman et al. described this entity as a benign, localized, hyperplastic, lymphoid mediastinal mass with "Hassall body-like" germinal centers and marked vascular proliferation (1). In 1969, Flendrig and Schillings described a histologic variant with large reactive follicles in dense fields of plasma cells and stressed an association with systemic symptoms (2). Subsequent cases with extramediastinal location, variable histologic features and clinical signs and manifestations were reported. In 1972, Keller et al. proposed two variants: hyaline vascular and plasma cell types (3). Subsequently, descriptions of multicentric Castleman's disease were published (4–7).

Recent studies have demonstrated an association of Castleman's disease with excess production of the cytokine IL-6. IL-6 is a pleiotropic, inflammatory cytokine produced by several cell types, including activated monocytes, B cells, endothelial cells, fibroblasts, and mesangial cells. A syndrome resembling multicentric Castleman's disease has been reported in mice transfected with an IL-6-producing recombinant retrovirus (8) and in mice transgenic for IL-6 under control of the immunoglobulin heavy-chain enhancer (9). Similarly, increased IL-6 production and IL-6 gene expression have been reported in patients with Castleman's disease (10–13). An increased production of this inflammatory cytokine also may be found in various other disorders, including systemic lupus erythematosus (SLE), AIDS, cardiac myxoma, multiple my-

eloma, and plasma cell leukemias (14). In all of these conditions, the elevations of IL-6 are associated with expansion of plasmacytes and increased production of immunoglobulins, some of which manifest autoimmune reactivity.

This report provides further evidence of an association among increased IL-6 production, Castleman's disease, and autoimmune manifestations. We present a child with clinical autoimmune disease resembling SLE and histopathologic features compatible with multicentric Castleman's disease. Increased levels of IL-6 in the serum and numerous cells with IL-6 gene expression in the lymph nodes were demonstrated. We propose that IL-6 measurements may be helpful in supporting a diagnosis of Castleman's disease.

CASE REPORT

A 21-month-old boy of African-American descent was evaluated for a generalized papular rash, which had been present since the age of 6 months. Generalized lymphadenopathy and splenomegaly were present. Peripheral blood cell count showed a mild increase in lymphocytes and platelets. Serum electrolytes, total protein, albumin, urea nitrogen, creatinine, alanine and aspartate aminotransferases, and lipids were normal. Serum lactate dehydrogenase (LDH) was elevated, at 1058 U/L. A PPD skin test was nonreactive, and a chest radiograph was normal. Urinalysis was normal. Serologies for HIV-1, syphilis, histoplasma, coccidioides, and blastomyces were negative. A skin biopsy showed an "unusual lymphohistiocytic infiltrate." Biopsy of a right axillary node (node 1) showed "reactive adenitis with marked follicular hyperplasia." Fungal and acid-fast stains were negative for organisms.

At 28 months of age, the patient was evaluated for the development of morning stiffness, joint pain, and intermittent fevers to 101°F. He had symmetric arthritis of the large joints of all extremities. The peripheral lymphocyte count was again mildly elevated, with some atypical lymphocytes. The platelet count was 533,000/mm^3, and the Westergren erythrocyte sedimentation rate (WESR) was 48 mm/hr. Antinuclear antibody (ANA) was positive in a speckled pattern (titer, 1:320). Repeat ANA performed with an autoantibody panel was positive at only 1:80. Normal (or negative) values were obtained for rheumatoid factor, CH50, HIV-2 serology, anti-double-stranded DNA antibody, antibodies to Ro (SS-A) and La (SS-B), anti-Sm, anti-RNP,

and anti-Scl-70 antibodies. Serologies for HIV-1, cytomegalovirus, and Epstein–Barr virus were negative. There were polyclonal elevations of total serum IgG (3,260 mg/dl), IgM (241 mg/dl), and IgA (208 mg/dl). Analysis of peripheral blood lymphocytes by flow cytometry showed an increase in absolute number and percentage of circulating B lymphocytes (1903 cells/mm^3). The ratio of helper (CD4)-to-suppressor (CD8) T cells was normal. Skull and long bone radiographs were normal. The patient took aspirin, 50 mg/kg/day, and returned to the clinic 1 month later with improvement of his arthritis.

At 3.5 years of age, the patient developed fatigue and a poor appetite. Polyarthritis and diffuse skin rash were unchanged, but lymphadenopathy had progressed. Nephritis was present, with hematuria, pyuria, and coarse granular casts in the urine. ANA was positive (titer, 1:160). Serum C3 and CH50 were low, at 45.8 mg/dl and 111 U, respectively, with normal C4 (16.6 mg/dl). Serum creatinine was 1.3 mg/dl, urea nitrogen was 39 mg/dl, and protein excretion was 1.1 g/24 hr. Kidneys were enlarged by ultrasound, with loss of corticomedullary differentiation. The patient had developed a microcytic, hypochromic anemia (hematocrit, 22%), with a reticulocyte count of 0.2%. Direct Coomb's test was positive for IgG. Marrow biopsy revealed mild erythroid hypoplasia, increased plasma cells, and adequate iron stores. Repeat node (node 2) and skin biopsies did not reveal any new findings. Renal biopsy specimen showed mesangial proliferative glomerulonephritis. Shortly after the patient began prednisone and azathioprine therapy, hypertension developed and was controlled with medication.

One month later, the patient developed seizures. Evaluation was negative, including head CT and MR scan, lumbar puncture, and 72-hr EEG. Blood pressure was well controlled. No metabolic derangements were found. Despite this, status epilepticus occurred 3 weeks later. A repeat MR scan showed an infarct in the right parietooccipital region. The hematocrit was improved at 28%, and the platelet count was 595,000/mm^3. Prothrombin time and partial thromboplastin time were normal. Anticardiolipin antibody and RPR were negative. Fungal serologies were negative, bacterial cultures of blood and cerebrospinal fluid remained negative, and the echocardiogram did not show any vegetations. Anticonvulsant therapy was continued for 1 year without further seizures, then discontinued.

The patient experienced rapid resolution of arthritis, skin rash, and splenomegaly on therapy.

There was an initial, gradual improvement of generalized lymphadenopathy and nephritis. Serum urea nitrogen has risen to 43–50 mg/dl, serum creatinine to 2.5–2.8 mg/dl, and WESR to 50 mm/hr. Serum C3 and C4 are normal and ANA has been negative for over 1 year.

METHODS

Histologic and Immunohistologic Techniques

B-5- or formalin-fixed tissue was paraffin embedded, cut to 3–5 μm, and stained with hematoxylin and eosin (H&E) and periodic acid Schiff (PAS). Other stains included Wright's (marrow aspirate), Prussian blue (marrow), Jones (kidney), methenamine silver (node), and fluorescent auramine O (node).

Specimens were prepared for electron microscopy as previously described (15).

Paraffin immunoperoxidase studies were performed on node biopsy (node 2) and skin biopsy specimens using the method described by Pinkus *et al.* (16). Sections were stained with monoclonal antibodies CD45 (HLe-1), CD20 (L26), CDw75 (LN1), CD45RO (UCHL-1), CD30 (Ber-H2), CD15 (Leu M1), and CD68 (KP1), and polyclonal antibodies directed against IgG, IgA, IgM, κ and λ, using a double-conjugated, peroxidase antiperoxidase method.

Flow Cytometry

Peripheral blood white cells and cell suspensions from node 2 were stained for surface fluorescence using rhodamine- or fluorescein-conjugated monoclonal antibodies and analyzed on a Becton Dickinson FACSCAN flow cytometer using standard procedures. Cells were reacted with monoclonal antibodies against CD45 (HLe), CD1 (OKT6), CD2 (Leu 5b), CD3 (Leu 4), CD4 (Leu 3a+3b), CD5 (Leu 1), CD8 (Leu 2a), CD10 (CALLA), CD20 (Leu 16), CD19 (CD19-B cell), CD25 (IL-2R), CD30 (RSC-1), HLA-DR, CD14 (Leu M3), CD33 (My9), CD34 (HPCA-1), and CD56 (Leu 19) and polyclonal antibodies against immunoglobulin light chains (Ortho Diagnostics, Raritan, NJ).

IL-6 Serum Assay

Serum IL-6 was determined in the B9 bioassay (17). The B9 cell line, an IL-6-dependent hybrid-

oma, was kindly provided by Dr. Lucien Aarden. Purified recombinant murine IL-6 (Genzyme, Cambridge, MA) was used as a standard. IL-6 activity is reported as picograms per milliliter in comparison with the standard. Serum IL-6 was also measured by enzyme immunoassay (EIA) performed by Specialty Laboratories, Inc. (Santa Monica, CA) using a Cytoscreen kit (Catalog ASYO3B, Biosource International, Camarillo, CA).

IL-6 in Situ Hybridization (ISH)

RNA probe was prepared using the 600-bp *Hind*III–*Dra*I fragment of IL-6 cDNA kindly provided by Dr. P. B. Sehgal, New York. The cDNA was inserted into the transcription vector pGEM-3Z (Promega, Madison, WI). Recombinant plasmids were linearized and transcribed with T7 or SP6 RNA polymerase to obtain antisense and sense probes, respectively, in the presence of ^{35}S-UTP. After transcription, the template was digested with DNase and the products were recovered by phenol extraction and ethanol precipitation. The specific activity was approximately 2×10^8 dpm/μg template.

A portion of node 2 was snap-frozen and stored at −70°C until use. Frozen sections (6 μm) were cut, mounted onto precleaned slides (Fisher Scientific, San Francisco, CA), fixed in 4% paraformaldehyde, washed in PBS, and transferred to 2× standard saline citrate (SSC). Hybridization was performed as described elsewhere (18). Specimens were dehydrated, air-dried, and covered with Kodak NTB nuclear track emulsion (Eastman-Kodak, Rochester, NY) for autoradiography. After exposure for 6–10 days at 4°C, the slides were developed, fixed, and counterstained with Giemsa. Cells were considered positive when there were more than 20 granules over the nucleus and cytoplasm. An adjacent tissue section hybridized with sense probe was used as a negative control for comparison.

RESULTS

Node biopsy specimens 1 and 2 showed similar findings. There was marked follicular hyperplasia extending from the cortex into the medulla (Figure 1a). Follicle size varied; most were large with a slightly irregular shape. Follicles were reactive, containing a mixture of transformed cells, cleaved cells, and histiocytes. Rare small follicles showed connective tissue deposition and hyalinized vessels.
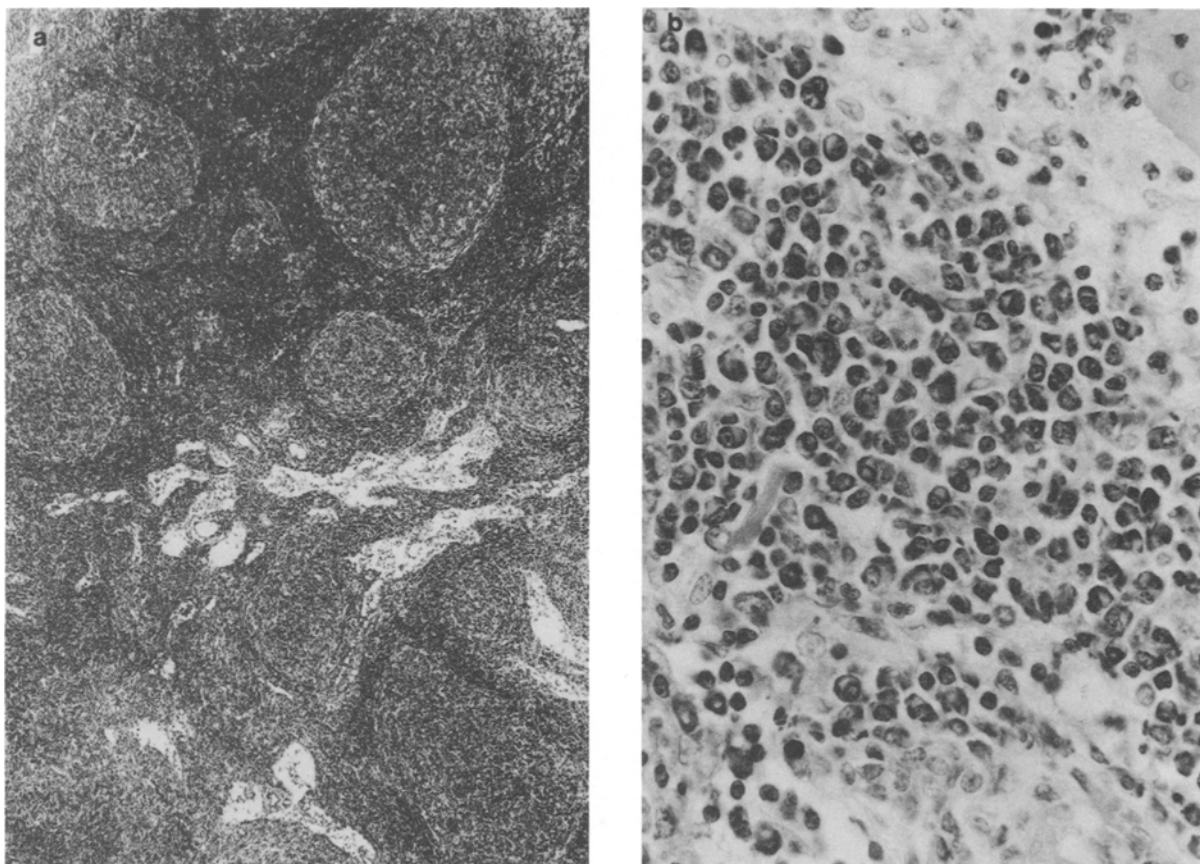
Fig. 1. (a) Low-magnification photomicrograph of node 2 demonstrating marked follicular hyperplasia. The follicles are predominantly large and reactive. The interfollicular areas are expanded by vascular proliferation. (b) Higher magnification reveals sheets of plasma cells in the interfollicular areas.

The interfollicular, paracortical, and medullary portions of the nodes had focal vascular proliferation. The interfollicular areas were expanded by lymphocytes, plasma cells, and occasional large transformed cells. In areas, the plasma cells were markedly increased and displayed a sheet-like growth pattern (Fig. 1b). Occasional plasma cells showed cytoplasmic immunoglobulin inclusions. Fluorescent auramine O and methenamine silver stains were negative for organisms.

Node 2 was analyzed by immunoperoxidase technique and showed that plasma cells marked polytypically with antibodies against immunoglobulin light chain. Flow cytometry of cells isolated from the node revealed a normal distribution of B and T cells.

The skin biopsies revealed a perivascular and periadnexal mild lymphocytic infiltrate which extended deep into the dermis. The epidermis was normal, without evidence of epidermotropism, hy-perkeratosis, or vacuolar degeneration of the basal layer. Paraffin immunoperoxidase studies performed on skin biopsy 1 revealed a predominance of T cells, and staining for CD30, seen in some childhood lymphomas, was negative.

Renal biopsy revealed a chronic, active, mesangial proliferative glomerulonephritis, characterized by heavy segmental mesangial proliferation with active and fibrous crescents. Strong granular mesangial staining for IgA, IgM, and C3 was noted by immunofluorescence. By electron microscopy, these were seen as numerous dense deposits in the mesangium, with some extension into endothelial regions of the capillary basement membrane. Reticular arrays were frequent in endothelial cells.

Marrow biopsy was normocellular, with an even distribution of myeloid and megakaryocytic elements. Some megakaryocytes had hyperlobulated nuclei. Erythroid elements were mildly decreased and iron was increased in a normal distribution.

There was a mild plasmacytosis (6.5%) with an occasional Mott cell.

IL-6 Serum Assay

Three specimens of the patient's serum, obtained at different points in time, were assayed for IL-6 activity. There was little or no IL-6 found in two specimens, but significant activity was found in one specimen. By the B9 bioassay, IL-6 was 517 ± 44 pg/ml, and by the EIA commercial assay, 42 pg/ml (reference range, <6 pg/ml). This level of IL-6 is well above normal serum values and in the same range reported in patients with active SLE and rheumatoid arthritis (19). All specimens were obtained while our patient was on prednisone and azathioprine therapy. The positive specimen was drawn during a hypertensive crisis, and serum IL-6 activity rapidly returned to low values when the patient was treated with high-dose prednisolone.

IL-6 in Situ Hybridization

A portion of node 2 was analyzed by ISH for the presence of IL-6 mRNA in cells. There were numerous, strongly positive cells located predominantly in the marginal zone of the lymph node. Scattered IL-6-expressing cells were occasionally found in the central parts and between lymphoid follicles. Figure 2 shows two areas of the lymph node (A and C). On top, the capsule and marginal sinus (S) are shown. Below, densely packed lymphoid cells form lymph nodules (N). Analyzed with dark-field technique (Figs. 2B and D), IL-6-expressing cells form clusters of white granules due to binding of "antisense" mRNA. They are located in the marginal sinus and expand radially, between lymphoid nodules into the medulla. In Fig. 2E, a marginal area (marked in Fig. 2C) is shown at a higher magnification. Figures 2G and H show an adjacent section of Figs. 2A and B but using a "sense" probe as a negative control. A rather homogeneous background without clusters of granules can be seen. These findings were consistent in several adjacent tissue sections and were confirmed by a second hybridization experiment.

DISCUSSION

Our patient's illness began in his first year of life. He had a generalized maculopapular skin rash, diffuse lymphadenopathy, splenomegaly, symmet-ric arthritis, and extraordinary polyclonal hyperglobulinemia by 28 months. He subsequently developed chronic glomerulonephritis and had an unexplained cerebrovascular accident. Serologic tests for syphilis, viral, or fungal infection were negative. Anticardiolipin antibodies were also negative. HIV was excluded as a possibility by several negative serologic screens and the finding of peripheral T cell counts that were not compatible with this disorder. SLE was considered a diagnostic possibility but was rejected on several counts: (i) The child had been ill since the first few months of life, when SLE is extraordinarily unusual; (ii) the skin rash and impressive peripheral lymphadenopathy were prominent early in the course and were more suggestive of Castleman's disease than SLE; and (iii) the patient never achieved a high titer of serum ANA or anti-double-stranded DNA antibody, and eventually the serum ANA became negative.

We considered that the patient might have a congenital lymphoproliferative syndrome similar to that occurring in MRL/lpr mice. Analysis of lymph node cell surface markers did not reveal the abnormal CD3+, CD4−, CD8− population characteristic of this condition (20). The striking similarities between our patient's clinical manifestations and the disease produced in mice by overexpression of the gene for IL-6 prompted us to look for IL-6 production in lymphoid tissue, since pretreatment serum was not available. The positive results by ISH for IL-6 led to consideration of whether our patient fits the spectrum of Castleman's disease.

Castleman's disease is a heterogeneous illness. Clinical features vary from a localized asymptomatic mass to multicentric involvement with prominent systemic features. Symptoms suggesting immune system activation, often with autoimmune features, may occur in the latter form. Unlike localized Castleman's disease, which remits after mass excision and tends to occur in younger patients (median age, 20), the multicentric form of Castleman's disease is a progressive or chronic disease and tends to occur in older patients (median age, 57) (5). Histologic findings in Castleman's disease are divided into hyaline vascular and plasma cell forms based upon lymph node histology, but there may be overlap of these features making subclassification difficult in some cases (21). Clinical features do not adhere strictly to histopathologic findings; patients with hyaline vascular type on biopsy may have systemic manifestations.
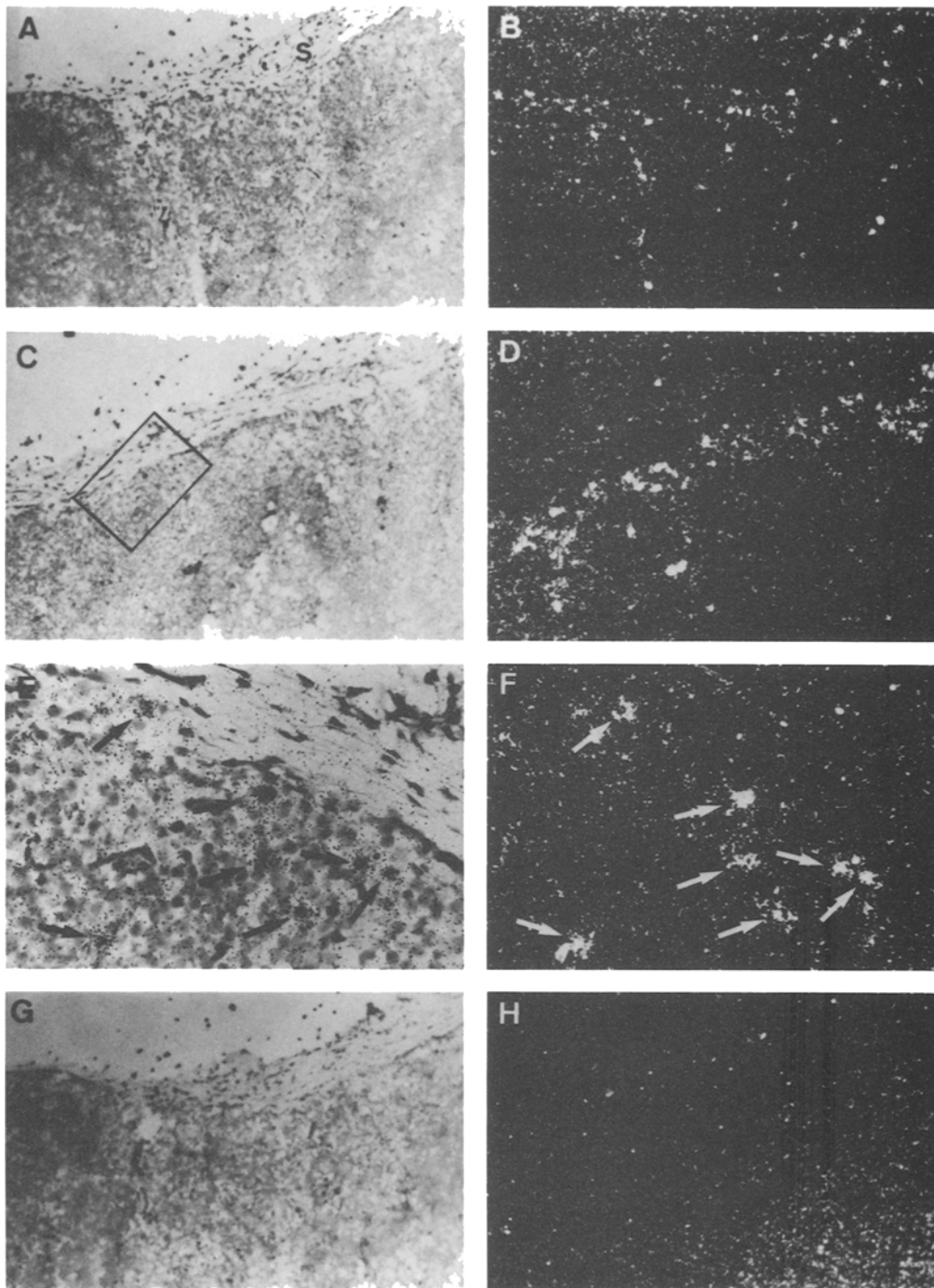
Fig. 2. A portion of node 2 analyzed by ISH for the presence of IL-6 mRNA. The panels on the left are standard photos (A, C, E, G), while those on the right are the corresponding dark-field photos (B, D, F, H). A shows the capsule, with the underlying marginal sinus (S) and lymphoid nodules (N) containing densely packed lymphocytes. In B, the IL-6-producing cells can be readily seen with their clusters of overlying white granules. A similar area of the node is shown in C and D. E and F show a high-power view of the portion of the node in C enclosed by the rectangle. Again, clusters of granules overlying IL-6-producing cells are readily seen (arrows). G and H, which lack clusters of granules, show an adjacent area of the node which was hybridized using a "sense" probe as a negative control.

Multicentric Castleman's disease is associated with generalized lymphadenopathy, hepatosplenomegaly, hemolytic anemia, polyclonal gammopathy, arthralgias, and skin lesions. Less frequently, thrombocytopenia, renal dysfunction, and neurologic abnormalities may occur (5). A vasoocclusive syndrome has been observed infrequently. This may be secondary to antiphospholipid antibodies or related to hyperviscosity (22).

The etiology of Castleman's disease remains unknown. Histologic features of the hyaline vascular type suggest a chronic reactive lymphoid hyperplasia although causal antigens or pathogens have not been found. The unusual blood vessels and germinal centers and the association with angiolipomas suggest that the hyaline vascular variant is a form of hamartoma (23). Various theories for the etiology of the plasma cell type include an abnormal immune reaction (24), a disorder of endothelial proliferation (25), and an expansion of autoantibody-producing plasma cells (26). The diagnosis of multicentric Castleman's disease can be difficult, particularly if germinal centers with hyaline vascular changes are not present. The differential diagnosis of the clinical and pathologic features includes hypersensitivity reactions, viral infections (including HIV), syphilis, angioimmunoblastic lymphadenopathy, several autoimmune disorders including SLE and rheumatoid arthritis, and lymphoid malignancies. Castleman's disease as an isolated clinical and histopathologic diagnosis is one of exclusion.

The histopathology of this patient's nodes is within the spectrum described for multicentric Castleman's disease. Both nodes demonstrated numerous reactive follicles, vascular proliferation in the interfollicular areas, and polyclonal sheets of plasma cells, although well-formed hyalinized follicles were not present. Changes described in SLE, such as paracortical foci of necrosis, hematoxylin bodies, and distension of the sinuses by histiocytes, plasma cells, and lymphocytes, were not seen.

Skin biopsy revealed a nonspecific dermal inflammatory lymphocytic infiltrate, located primarily in a perivascular and periappendageal distribution. The epidermis was normal. Skin lesions have been reported in up to 55% of patients with Castleman's disease (27) and have been variously described as erythematous maculopapular, toxic erythema, or nodular.

Renal biopsy in this patient showed chronic, active mesangial proliferative glomerulonephritis. This pattern is similar to that seen in Henoch–

Schönlein purpura, severe IgA nephropathy, or, occasionally, SLE. Henoch–Schönlein purpura and IgA nephropathy were not compatible with the clinical features of this patient, and SLE was not favored for the reasons mentioned earlier. Identical histopathology is described in mice with genetically engineered IL-6 excess. Elevated levels of urine IL-6 occur in mesangial nephropathy (28) and in the serum in Castleman's disease (10–12). Renal manifestations such as minimal change nephropathy (29), membranous nephropathy (30), and proliferative glomerulonephritis (31) have been described in Castleman's disease, although this is not a common feature.

An association of Castleman's disease with excess production of IL-6 is supported by both clinical studies and animal models of unregulated IL-6 production (8, 9). IL-6 is a pleiotropic cytokine, with a panoply of biologic effects (14, 32). It is produced by a wide range of cells, including monocytes, endothelial cells, B lymphocytes, fibroblasts, keratinocytes, and myeloma cells. Most of the cell types which produce IL-6 do so in response to stimuli such as exogenous IL-6 and TNF; the IL-6 promoter is known to be rapidly activated by these cytokines (14). IL-6 is a plasmacytoma growth factor, a differentiation factor for B lymphocytes, and a stimulator of hepatocyte production of acute phase proteins. It acts synergistically with IL-2, IL-1, or TNF to promote the proliferation and differentiation of cytotoxic T lymphocytes, and acts synergistically with IL-3 to sustain the proliferation of progenitor cells in the marrow. It has been shown to promote the proliferation of mesangial cells (28) and, thus, is implicated in the pathogenesis of proliferative mesangial glomerulonephritis.

Various patterns of IL-6 production have been described in nodes from patients with Castleman's disease. Yoshizaki et al. have demonstrated increased IL-6 production in nodal tissue of two patients with Castleman's disease using in vitro culture and immunohistologic techniques (10). Leger-Ravet et al. found increased IL-6 gene expression in the follicles of the lymph nodes of two patients with localized Castleman's disease and systemic symptoms, but exclusively in the interfollicular areas of the lymph nodes of a total of six patients with various forms of the disease, including four with multicentric disease and systemic symptoms (11). In a study by Hsu et al., IL-6 was abundantly expressed by cells in the hyperplastic germinal centers in the plasma cell form of Castle-

man's disease but was not detected in germinal centers in patients with the hyaline vascular form of the disease (12). IL-6 expression in germinal centers of Castleman's disease has been variously localized to IgD⁻ B cells (10) or to follicular dendritic cells (11). In settings of inflammatory lymphoid hyperplasia, IL-6 mRNA is found primarily in histiocytes, and not in germinal center cells (33). The localization of IL-6 hybridizing cells in the node of our patient was similar to that described in multicentric Castleman's disease by Leger-Ravet et al. (11).

Unregulated excessive production of IL-6 in mice produced a constellation of features very similar to those of our patient. These animals had generalized lymphadenopathy, massive splenomegaly, hypochromic microcytic anemia, thrombocytopenia, hypoalbuminemia, polyclonal hypergammaglobulinemia, and hyperfibrinogenemia. Node biopsy revealed almost-complete replacement of nodal tissue by mature plasma cells. However, the follicles in the nodes of the mice were atretic, in contrast to the hyperplasia seen in Castleman's disease. The marrow showed an increased number of mature granulocytes, increased macrophages, and occasional plasma cells. Kidneys had glomerular enlargement from an increase in mesangial cells and matrix. These data support a role for IL-6 in the promotion of the histopathologic and clinical features seen in Castleman's disease. Our patient's lymph nodes showed plasmacytosis, but with follicular hyperplasia rather than atresia. His bone marrow showed a similar increase in plasma cells. Renal biopsy was remarkably similar to that described in IL-6-producing mice.

Castleman's disease has been reported in approximately 80 children and adolescents. In a recent review, only 12 cases were 13 years old or younger (34). Not included in this review are a 2-month-old female with supraclavicular node involvement (35), a 4-month-old male with axillary node involvement described as angiomatous hamartoma (36), and an 11-year-old Taiwanese male with involvement of the mesenteric root (37). All cases in children presented as localized disease, although constitutional symptoms, including anemia, growth delay, splenomegaly, night sweats, and fevers, have occurred (38–46). Despite the presence of splenomegaly in some cases, it is unlikely that these represented cases of multicentric Castleman's disease, as resolution of all symptoms occurred after resection of the local tumor (38).

CONCLUSION

In summary, we report a young child whose unusual presentation is most consistent with a diagnosis of multicentric Castleman's disease, although his autoimmune manifestations resemble those seen in patients who have SLE. The presence of IL-6 production in node tissue and the evidence of overproduction of IL-6 in the serum of this patient during illness support the concept that IL-6 may be responsible for his constellation of symptoms and pathologic findings.

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