

Letter to the Editor

Polymorphous lymphoproliferative disorder with Hodgkin-like features in common γ -chain-deficient severe combined immunodeficiency*To the Editor:*

Severe combined immunodeficiencies (SCIDs) are inherited T-lymphocyte differentiation disorders.¹ Most patients present with persistent respiratory or gastrointestinal infections; lymphoproliferation is not recognized as a presenting feature. We describe IL-2 receptor γ -chain deficiency presenting with polymorphous lymphoproliferative lesions.

Immunologic parameters and mutation analysis were measured as previously described.^{2,3} Paraffin-embedded tissue block sections were stained with hematoxylin and eosin. Immunohistochemistry was performed by using the Dako Autostainer (Dako UK Ltd, Ely, Cambridgeshire, United Kingdom) or the BioGenex i6000 Automated Staining System (Launch Diagnostics Limited, San Ramon, Calif). Antibodies from various manufacturers were used with the Menapath X-Cell Plus HRP Polymer detection system (A. Menarini Diagnostics, Wokingham, United Kingdom). *In situ* hybridization was performed by using the Ventana Benchmark XT and Ventana ISH iVIEW Blue Detection Kit reagents (Ventana Medical Systems Inc, Tucson, Ariz).

The first patient, with a c.676C>T mutation in exon 5 of interleukin-2 receptor γ (*IL2RG*), presented with pneumocystis pneumonia and a large cranial soft tissue lesion, predating his respiratory illness by 2 months. During excision, a small extracranial and larger intracranial component were noted with some bone erosion and thickened, infiltrated dura mater, but no cerebral infiltration. He died from pulmonary hemorrhage after an unconditioned 10/10 HLA antigen-matched maternal bone marrow infusion.

The second child with IVS3-11bp C>G 11 bases into the *IL2RG* intron 3 splice acceptor site presented with hepatomegaly and jaundice. Chest radiography demonstrated a lytic lesion in the left third rib with no lung involvement. Ultrasonic examination revealed a 1-cm lesion in the left hepatic lobe and multiple splenic lesions. A left axillary erythematous indurated area in the subcutis was excised at the time of rib biopsy, bone marrow aspiration, and trephine biopsy.

The lymphoproliferative lesions cleared after an unconditioned 10/10 HLA antigen-matched unrelated donor bone marrow infusion; more than 10 years posttransplant, he has 94% donor T lymphocytes, 14% donor B lymphocytes, and 10% donor myeloid chimerism with ongoing thymopoiesis.

The mass from patient 1 contained small flecks of calcification. The intracranial component compressed but did not infiltrate the frontal lobe. Histology showed a polymorphous cellular infiltrate including lymphocytes arranged mostly in sheets, plasma cells (including frequent binucleate forms and many with Dutcher bodies), plasmacytoid cells, histiocytes, and fibroblasts with associated fibrosis. Small numbers of polymorphs were seen. Scattered within this mixed cellular population were large bizarre cells with vesicular nuclei, many with multiple nucleoli, similar in appearance to Hodgkin Reed-Sternberg (HRS) cells; medium-sized cells of similar morphology, usually mononuclear, were frequent and arranged mainly in nodules scattered at random

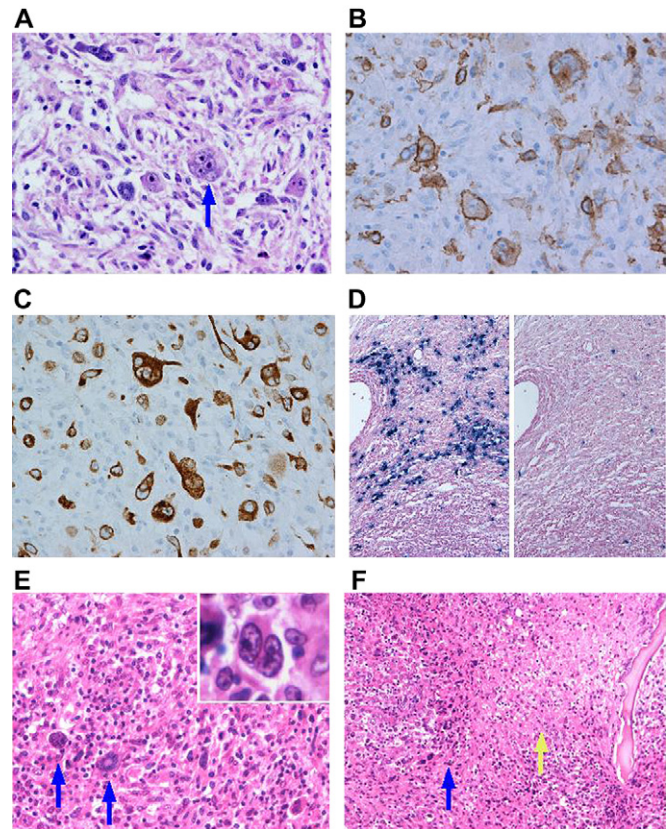


FIG 1. Morphologic and phenotypic characteristics of lymphoproliferative lesions from patients 1 and 2. **A-D**, Patient 1. **A**, Hematoxylin and eosin-stained preparation. Large cells with copious cytoplasm and large vesicular nuclei and prominent nucleoli, set in a background of reactive cells including histiocytes, fibroblasts, and lymphocytes. Some multinucleate forms are seen (arrow), which resemble HRS cells. **B**, Immunostaining for CD30. Note the intense membrane staining of the large neoplastic cells. **C**, Immunostaining for the B-lymphocyte-associated antigen CD79a. Note the intense cytoplasmic labeling of tumor cells. **D**, *In situ* hybridization for immunoglobulin light-chain mRNA. The 2 pictures represent the same area, and a blood vessel is represented on the left to highlight this. There are many more κ -positive cells than λ . Note that these are small lymphoid cells. The large cells shown in **A** to **C** did not express immunoglobulin light chains. **E and F**, Patient 2. **E**, Hematoxylin and eosin-stained preparation. Large cells with large hyperchromatic nuclei are set in a background of reactive cells including histiocytes, fibroblasts, and lymphocytes. Multinucleate forms were seen, and some cells of more typical HRS cell morphology were also present (inset). **F**, Hematoxylin and eosin-stained preparation. In this lower-power view, extensive tumor necrosis is demonstrated (yellow arrow). The bony trabeculum on the right is also necrotic. The blue arrow indicates a band of large neoplastic cells with hyperchromatic nuclei at the edge of the necrotic zone. (Original magnification $\times 400$ except **D** and **F**, which were original magnification $\times 200$.)

within the tissue, most frequently in fibroblast-rich and histiocyte-rich zones. Extensive necrosis with associated zones of dystrophic calcification was present; associated histiocytes including foreign body giant cells were conspicuous.

Immunohistochemistry (Fig 1, A-D) showed that the large atypical cells and their medium-sized counterparts were strongly CD20⁺, CD79a⁺, CD30⁺, and CD15⁺, the last focally. CD45 and CD3 were negative. Epithelial membrane antigen was negative. The population of small lymphoid cells showed a heavy

predominance of B lymphocytes (CD20⁺, CD79a⁺) over T lymphocytes (CD3⁺, CD2⁺), the latter present in small numbers only. *In situ* hybridization for immunoglobulin light-chain mRNAs showed a large patch of κ ⁺ cells, with almost complete absence of λ expression. Ki67 labeled many large and medium-sized cells, whereas the proliferation fraction in the small B-lymphocyte population was low. Numerous CD68⁺ histiocytes were present. Immunostaining for EBV latent membrane protein and human herpes virus 8 was negative. *In situ* hybridization for EBV-encoded RNA mRNAs 1 and 2 was negative. At autopsy, hepatic and pulmonary tumor deposits with similar morphology to that described were found.

Histology from patient 2 (Fig 1, E and F) showed a destructive tumor, involving bone with extension into subcutaneous fat and dermis, and composed of numerous large cells with large nuclei, some with a hyperchromatic appearance, and others appearing vesicular with prominent nucleoli. Many multinucleated forms were identified, resembling HRS cells (Fig 1, E). The large neoplastic cells were set in a background of an admixture of cells including histiocytes, lymphocytes, and fibroblasts. There was extensive tumor-associated necrosis, also involving bony trabeculae (Fig 1, F).

The large neoplastic cells were CD30⁺, CD79a⁺. EBV was negative by immunohistochemistry (for EBV latent membrane protein) and *in situ* hybridization (for EBV-encoded RNA mRNA types 1 and 2). The large cells were negative for CD45, CD15, epithelial membrane antigen, anaplastic lymphoma kinase, CD20, CD3, CD4, CD5, CD7, CD8, granzyme B, perforin cytomegalovirus, CD43, and human herpes virus 8. The small lymphocyte population was predominantly of CD20⁺ B-lymphocyte type; a minority was CD3⁺. Bone marrow aspirate and trephine revealed no lymphocytes or malignant cells. In both cases, stains for mycobacteria and fungi were negative. We consider that these tumors are a polymorphic lymphoproliferative disorder with Hodgkin-like features.

Patients with SCID generally present with persistent infection; lymphoproliferation has rarely been reported in this context. EBV-associated lymphoma has been reported in 5 adenosine deaminase-deficient patients with SCID treated with polyethylene glycol-conjugated adenosine deaminase, thought to be a result of incomplete immune reconstitution with associated T lymphopenia.⁴⁻⁶ There is only 1 previous report of lymphoma in an *IL2RG*-deficient patient with SCID. A 7-month-old child presented with a retro-orbital EBV-negative diffuse large-cell B-lymphocyte non-Hodgkin lymphoma.⁷

Lymphoproliferative disorders developing in primary immunodeficiency are usually classifiable according to entities arising in immunocompetent individuals, often associated with EBV. In *IL2RG*-deficient SCID, tumors such as those described have not previously been reported. In each patient, presentation was extranodal and exhibited extensive necrosis. Both showed large HRS-resembling cell populations expressing CD30 and CD79a (and also CD20 and CD15 in case 2), in a background of histiocytes, fibroblasts, and lymphoid cells, predominantly B lymphocytes, the latter population showing focal plasma cell differentiation and light-chain restriction in case 1. There are several morphologic and phenotypic features resembling Hodgkin lymphoma, but extranodal presentation, extensive necrosis, and B-lymphocyte population with plasma cell differentiation (case 2) are inconsistent. The tumors described here share features

with polymorphous posttransplant lymphoproliferative disease,⁸ in which extranodal presentation, necrosis, HRS-like cells, and B-lymphocyte proliferation with plasma cell differentiation are described. Similar lymphoproliferative disorders, usually EBV-associated, are seen in association with iatrogenic immunosuppression such as that occurring in methotrexate therapy.⁹

We conclude that Hodgkin-like polymorphous lymphoproliferative disorder is a rare presentation of lymphoid abnormalities in SCID.

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Mary A. Slatter, MD^{a,e}

Brian Angus, FRCPATH^b

Kevin Windebank, MD^c

Alison Taylor, MSc^d

Cathy Meaney, BSc^d

Tracey Lester, FRCPATH^d

Gail Norbury, FRCPATH^d

Sophie Hambleton, MD^{a,e}

Mario Abinun, MD^{a,e}

Terence J. Flood, MD^a

Andrew J. Cant, MD^{a,e}

Andrew R. Gennery, MD^{a,e}

From the Departments of ^aPaediatric Immunology, ^bPathology, and ^cPaediatric Oncology, Newcastle Upon Tyne Hospital, NHS Foundation Trust; ^dMolecular Genetics, Great Ormond Street Hospital, NHS Trust, London, United Kingdom; and ^ethe Institute of Cellular Medicine, Newcastle University, Newcastle Upon Tyne, United Kingdom. E-mail: a.r.gennery@ncl.ac.uk.

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