First Reported Cases of Intravascular Large Cell Lymphoma of the NK Cell Type

Clinical, Histologic, Immunophenotypic, and Molecular Features

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Abstract

Most cases of intravascular large cell lymphoma are of B-cell phenotype, with a few cases of T-cell lineage and rare cases with histiocytic features described. A definitive natural killer (NK) cell variant has not been recognized. This report is the first to describe the clinical, histologic, immunophenotypic, and molecular features of 2 cases of intravascular lymphoma with an NK cell phenotype (CD3ε+, CD2+, CD7+, CD56+, T-cell intracytoplasmic antigen-1+ (TIA-1), perforin+, granzyme B+, CD20–, CD4–, CD5–, CD8–, T-cell receptor [TCR] βF1–). Molecular studies for TCR *gene rearrangements revealed a germline configuration. A 41-year-old man had erythematous plaque-like subcutaneous lesions of the lower extremities in which biopsy revealed Epstein-Barr virus–positive intravascular lymphoma. Following chemotherapy and stem cell transplantation, he was alive with no evidence of disease at 1 year. A 47-year-old woman had myalgias, arthralgias, weakness, fever, altered mental status, and pancytopenia. Bone marrow biopsy demonstrated intravascular lymphoma. Therapy was initiated; however, her condition deteriorated rapidly, and she died. Autopsy revealed involvement of multiple organs, including brain, kidneys, ovaries, and bone marrow. These cases represent the first documented examples of an NK cell variant of intravascular lymphoma.*

Intravascular large cell lymphoma (IVL) is a rare disorder characterized by the presence of large neoplastic lymphoid cells restricted to the lumens of small vessels, particularly capillaries. This disorder was first described as angioendotheliomatosis proliferans systemisata by Pfleger and Tappeiner[1] in 1959. The neoplastic cells initially were believed to be of endothelial origin. Subsequent immunohistochemical and molecular studies demonstrated the lymphoid nature of the neoplastic cells.[2-6] IVL usually is disseminated widely in extranodal sites. Skin and central nervous system (CNS) are most frequently involved.[7-9] More than 200 cases have been reported, most of which are of B-cell phenotype and are regarded as rare variants of extranodal diffuse large B-cell lymphoma in the World Health Organization classification.[8] A few cases of T-cell lineage[7,10-14] and rare tumors with histiocytic features have been described.[15,16] Epstein-Barr virus (EBV) has been identified in the neoplastic cells in some cases, mainly T-cell type.[14,17] To our knowledge, cases of IVL of definitive natural killer (NK) cell type have not been reported, although a case of NK-like IVL has been described.[18] We describe 2 cases of a previously unrecognized variant of IVL that exhibits an NK cell phenotype.

Case Reports

Case 1

A 41-year-old man sought care because of a several month history of erythematous, plaque-like, firm, subcutaneous lesions involving the left lower extremity and the right thigh, unassociated with other clinical findings, or constitutional

symptoms. The lesions were not painful or pruritic. The results of all laboratory and radiologic studies, including CBC count, liver function tests, computed tomography scan and magnetic resonance imaging (MRI) of the brain, were unremarkable except for a mild increase in the C-reactive protein level. His medical and family histories were unremarkable. The right thigh lesion was biopsied excisionally and revealed features of IVL of the NK cell type. Bone marrow biopsy and aspirate revealed no evidence of tumor involvement. Following combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisone (also known as CHOP) and stem cell transplantation, the patient was alive with no evidence of disease at 1 year.

Case 2

A 47-year-old woman had a 2-week history of myalgia, arthralgia, weakness, and fever (temperature more than 40.6°C [105°F]). On admission, she had altered mental signs, including confusion, and pancytopenia. An MRI of the brain revealed microvascular ischemic changes. A bone marrow biopsy demonstrated IVL of the NK cell type. Therapy was initiated; however, the patient's condition rapidly deteriorated, and she died 15 days after admission. An autopsy was performed.

Materials and Methods

Immunoperoxidase studies were performed on paraffin-embedded sections as previously described.[19,20] Antibodies and methods used are summarized in **Table 1**. In situ hybridization studies were performed on paraffin-embedded sections using a fluorescein-conjugated oligonucleotide probe for detection of messenger RNA sequences of EBV (EBV-encoded RNA [EBER]) (Novocastra Laboratories, Newcastle upon Tyne, England), as previously described.[21]

DNA was isolated from paraffin-embedded tissue samples and analyzed by polymerase chain reaction (PCR) technique. Two separate aliquots of DNA were amplified in parallel using

Table 1
Antibodies Evaluated in Paraffin Sections

Antibody to*	Major Immunoreactivity Profile	Source†	Titer	Pretreatment
CD2 (clone AB75)	Peripheral T cells, NK cells, thymocytes	Novocastra	1:600	Steamer/EDTA
CD3ε				
Polyclonal	Pan T cell, NK cells	DakoCytomation	1:400	Steamer/EDTA
Clone SP7, rabbit	Pan T cell, NK cells	Lab Vision	1:150	Steamer/citrate buffer
CD4 (clone 4B12)	Helper/inducer T cells, thymocytes, monocytes (subset)	Novocastra	1:800	Steamer/EDTA
CD5 (clone 4C7)	Pan T cell, mature B cell (subset)	Novocastra	1:200	Steamer/EDTA
CD7 (clone CD7-272)	Mature T cells, NK cells, thymocytes	Novocastra	1:50	Steamer/citrate buffer
CD8 (clone C8/144B)	Suppressor/cytotoxic T cells, NK subsets, thymocytes	DakoCytomation	1:100	Steamer/EDTA
CD20 (clone L26)	Pan B cell	DakoCytomation	1:500	Steamer/target unmasking fluid
CD30 (clone Ber-H2)	Activated T and B cells, Reed-Sternberg cells	DakoCytomation	1:25	Steamer/DAKO retrieval solution
CD34 (clone QBend-10)	Endothelial cells, stem cells, blasts	Beckman Coulter	1:50	Steamer/citrate buffer
CD43 (clone leu-22)	T cells, B-cell subset, NK cells, myeloid cells, histiocytes	Becton Dickinson	1:1,000	Steamer/EDTA
CD56 (clone 123C3.D5)	NK cells, T-cell subset, neural/neuroendocrine marker	Cell Marque	1:20	Steamer/EDTA
Perforin (clone P1-8, rat)	NK cells, activated cytotoxic T cells (cytoplasmic cytotoxic granules)	DakoCytomation	1:100	Steamer/EDTA
CD57 (clone HNK-1)	NK cells (subset), T-cell subset, neuroendocrine cells	Becton Dickinson	1:100	No pretreatment
TIA-1 (clone TIA-1)	NK cells, T cells subset (cytoplasmic cytotoxic granules)	DakoCytomation	1:2,000	No pretreatment
TCRβF1 (clone 8A3)	T cells (TCRβ chain constant region)	Endogen	1:80	Pronase
Granzyme (clone GrB-7)	NK cells, activated cytotoxic T cells (cytoplasmic granules)	Biodesign International	1:10	Steamer/EDTA
Lymphatic endothelium (clone D2-40)	Lymphatic endothelium	Signet	1:100	Steamer/citrate buffer
Factor VIII–associated antigen (polyclonal)	Endothelial cells, megakaryocytes	DakoCytomation	1:1,000	Trypsin
Lysozyme (polyclonal)	Myeloid cells, monocytes, macrophages	DakoCytomation	1:4,000	Trypsin
Myeloperoxidase (polyclonal)	Myeloid cells	DakoCytomation	1:8,000	No pretreatment
Keratin proteins (clones AE1/AE3)	Normal and neoplastic epithelial cells	Boehringer-Mannheim	1:1,000	Steamer/EDTA

NK, natural killer; TCR, T-cell receptor; TIA-1, T-cell intracytoplasmic antigen-1.
* All polyclonal antibodies are rabbit antibodies.
† Novocastra, Newcastle upon Tyne, England; DakoCytomation, Carpinteria, CA; Lab Vision, Fremont, CA; Beckman Coulter, Miami, FL; Becton Dickinson, San Jose, CA; Cell Marque, Hot Springs, AR; Endogen, Woburn, MA; Biodesign International, Saco, ME; Signet, Dedham, MA; Boehringer-Mannheim, Indianapolis, IN.

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4 sets of primers, V_γ1-8, V_γ9, V_γ10, and V_γ11, to the variable and joining regions of the T-cell receptor (*TCR*) γ chain gene. Analysis of the amplified product by a denaturing gradient gel electrophoresis technique was performed.

Results

The biopsy of the right thigh lesion (case 1) revealed large atypical lymphoid cells with irregular nuclei with prominent nucleoli and moderate amounts of pale cytoplasm in many blood vessels in the dermis and subcutaneous tissue **Image 1A** and **Image 1B**. Involvement was restricted to the vascular lumens. Immunophenotypic studies on paraffin sections revealed that the neoplastic cells were reactive for CD3ε **Image 1C**, CD56 **Image 1D**, CD2, CD7, CD43 (subset), bcl-2, T-cell intracytoplasmic antigen-1 (TIA-1), and perforin **Image 1E** but negative for CD20, CD5, CD4, CD8, TCRβF1 **Image 1F**, CD30, lysozyme, myeloperoxidase, and keratin proteins. An in situ hybridization study for EBV (EBER) exhibited nuclear positivity for the lesional cells **Image 1G**. The endothelial lining cells of the involved vessels exhibited reactivity for factor VIII–associated antigen and CD34 **Image 1H**. Lymphatic channels (D2-40+) were devoid of tumor cells. PCR analysis of the paraffin-embedded tissue for *TCR* gene rearrangements demonstrated no clonal T-cell populations **Image 2**. Overall findings supported a diagnosis of an EBV-positive IVL of the NK cell type.

In case 2, the diagnosis of IVL was made on the basis of a bone marrow biopsy in which vascular channels were distended by an accumulation of large malignant lymphoid cells with oval nuclei and a moderate amount of cytoplasm **Image 3A**. Immunophenotypically, the neoplastic cells were strongly positive for CD2, CD3ε **Image 3B**, CD7 **Image 3C**, CD56 **Image 3D**, TIA-1, and granzyme B and negative for B-cell markers, including CD20, and for CD5, CD4, CD8, and CD57.

Autopsy revealed involvement of multiple organs by IVL, including the brain, pituitary, bone marrow, kidneys, ovaries, and cervix. The brain was involved extensively, as exemplified in a section of pituitary gland **Image 4A**, and revealed multiple small infarcts. The lungs were not involved. The liver and spleen exhibited extensive infarct-type necrosis, precluding definitive assessment of tumor involvement. At autopsy, many tumor cells appeared apoptotic. In some vessels, the neoplastic cells appeared entrapped in a fibrin meshwork. Tumor cells in the involved autopsy tissues revealed the same phenotype as that apparent for the bone marrow infiltrate, including reactivity for CD7 **Image 4B**, TIA-1 **Image 4C**, and granzyme B **Image 4D**. Studies for EBV (latent membrane protein and EBER) were negative. Molecular studies (PCR) of paraffin-embedded tissue samples were negative for immunoglobulin and α/β and γ/δ *TCR* gene rearrangements. These findings supported a diagnosis of IVL of the NK cell phenotype.

The clinical, immunophenotypic, and molecular studies of the 2 cases of IVL of the NK cell type are summarized in **Table 2**.

Discussion

IVL is an unusual subtype of extranodal large cell lymphoma that generally is a systemic disease with a predilection for skin and CNS involvement.[8,22-24] This disorder usually affects older patients (age range, 34-85 years; mean, 65 years) with a slight male predominance. Skin lesions most often consist of tender erythematous subcutaneous nodules, as noted in our case 1, as well as telangiectasia, cellulitis, and lymphedema. Protean neurologic findings might occur, including dementia, nonlocalizing defects, polyneuropathy, myalgia, and muscle weakness. Other clinical findings include fever, anorexia, weight loss, malaise, and signs and symptoms reflecting the microvascular occlusions at various sites, particularly the skin and brain.

The clinical picture might be confusing, often compromising prompt and accurate diagnosis of this unusual disorder. CNS involvement was a prominent feature in one of our patients (case 2). In that case, MRI demonstrated microvascular ischemic changes and the autopsy revealed extensive CNS disease with multiple small infarcts. Although often fatal, especially in patients with CNS involvement, patients with IVL that is diagnosed early and treated with aggressive chemotherapy might achieve remission as apparent in one of our patients (case 1) and even long-term disease-free survival.[22,23]

In addition to CNS disease, other common sites of involvement found at autopsy include bone marrow, adrenal, prostate, and kidney. Renal involvement might be associated with nephrotic syndrome.[25] Prominent pulmonary involvement is unusual and was not observed at autopsy in our patient who died. Rare cases have been described in immunosuppressed patients, including patients with AIDS or after transplantation. In 1 patient with AIDS, IVL was described within Kaposi sarcoma lesions.[17] Rarely, vascular channels within cutaneous hemangiomas might exhibit IVL.[24,26] Hematologic findings include pancytopenia, as noted in case 2, isolated anemia, thrombocytopenia or leukopenia, and autoimmune hemolytic anemia and diffuse intravascular coagulation.

As in case 2, the initial diagnosis might be made by bone marrow biopsy in a patient with confusing systemic and/or CNS symptoms.[27] The presence of lymphoma cells in bone marrow sinusoidal vessels might be subtle and easily overlooked; however, immunohistochemical studies for lymphoid markers readily permit detection of tumor cells. Despite the intravascular predilection of the tumor cells, peripheral blood

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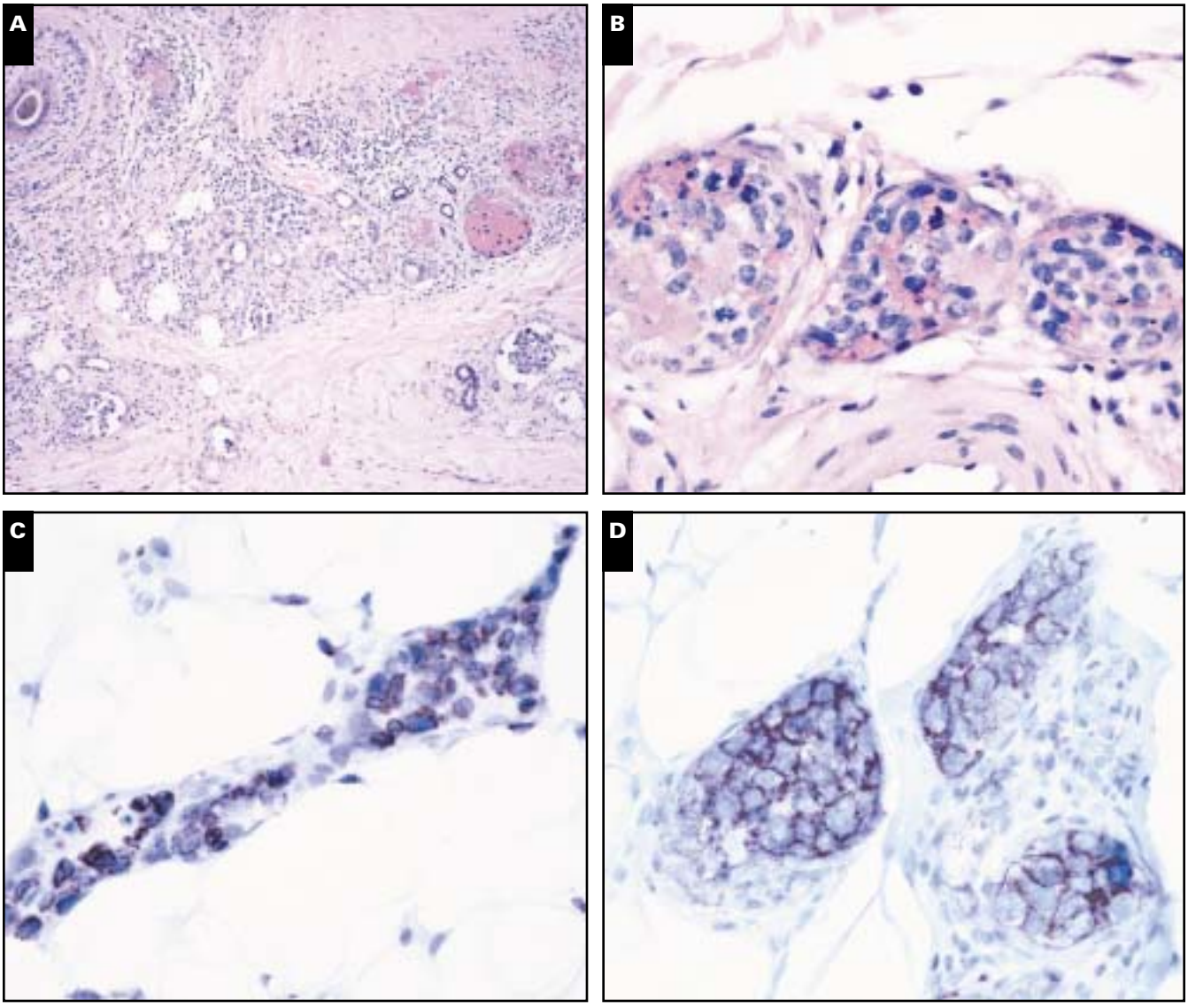

Image 1 (Case 1) Skin biopsy, paraffin section. **A**, Large atypical lymphoid cells in the dermis and subcutaneous tissue demonstrated an intravascular distribution (H&E, ×100). **B**, Higher magnification revealed vascular channels distended by tumor cells with associated fibrin thrombi (H&E, ×400). **C-G**, The neoplastic cells revealed a natural killer cell phenotype and were CD3ε+ (**C**), CD56+ (**D**), perforin+ (**E**), T-cell receptor βF1– (**F**), and Epstein-Barr virus–encoded RNA+ (**G**) (**C-F**, immunoperoxidase, hematoxylin counterstain, ×400; **G**, in situ hybridization, methyl green counterstain, ×400).

involvement is unusual. A few cases of IVL, predominantly in Asian patients, have been associated with hemophagocytic syndrome.[28-31] The latter cases are characterized by the absence of skin lesions, rarity of neurologic symptoms, frequent bone marrow involvement, and hepatosplenomegaly and could represent a distinct variant of IVL.[30]

A review of reported cases of IVL revealed that approximately 85% to 90% are of a B-cell lineage and 10% to 15% are of a T-cell origin, although the incidence of T-cell IVL cases reported in the literature might be overestimated.[7-17,22-24,27-33] Owing to the rarity of T-cell IVL cases, they are more likely to be reported. Also, reported cases of presumptive T-cell type with expression of CD45RO or/and CD43 as the sole evidence of T-cell origin might not represent true T-cell neoplasms[10,33] and possibly could be of NK cell derivation. Additional studies would be required for definitive evaluation and classification. Only rare cases have been reported with histiocytic features.[15,16]

Neoplastic cells of most IVL cases are reactive for bcl-2, with at least 25% positive for bcl-6.[24,34] Most cases are negative for CD5 and CD10; however, cases with both markers have been described.[24,31,34] Molecular studies have been done in a limited number of cases, and most have shown immunoglobulin heavy chain gene rearrangements, supporting a postfollicular B-cell origin.[24,35,36] Studies for *bcl*-2 gene rearrangement have been negative. Cytogenetic studies in the

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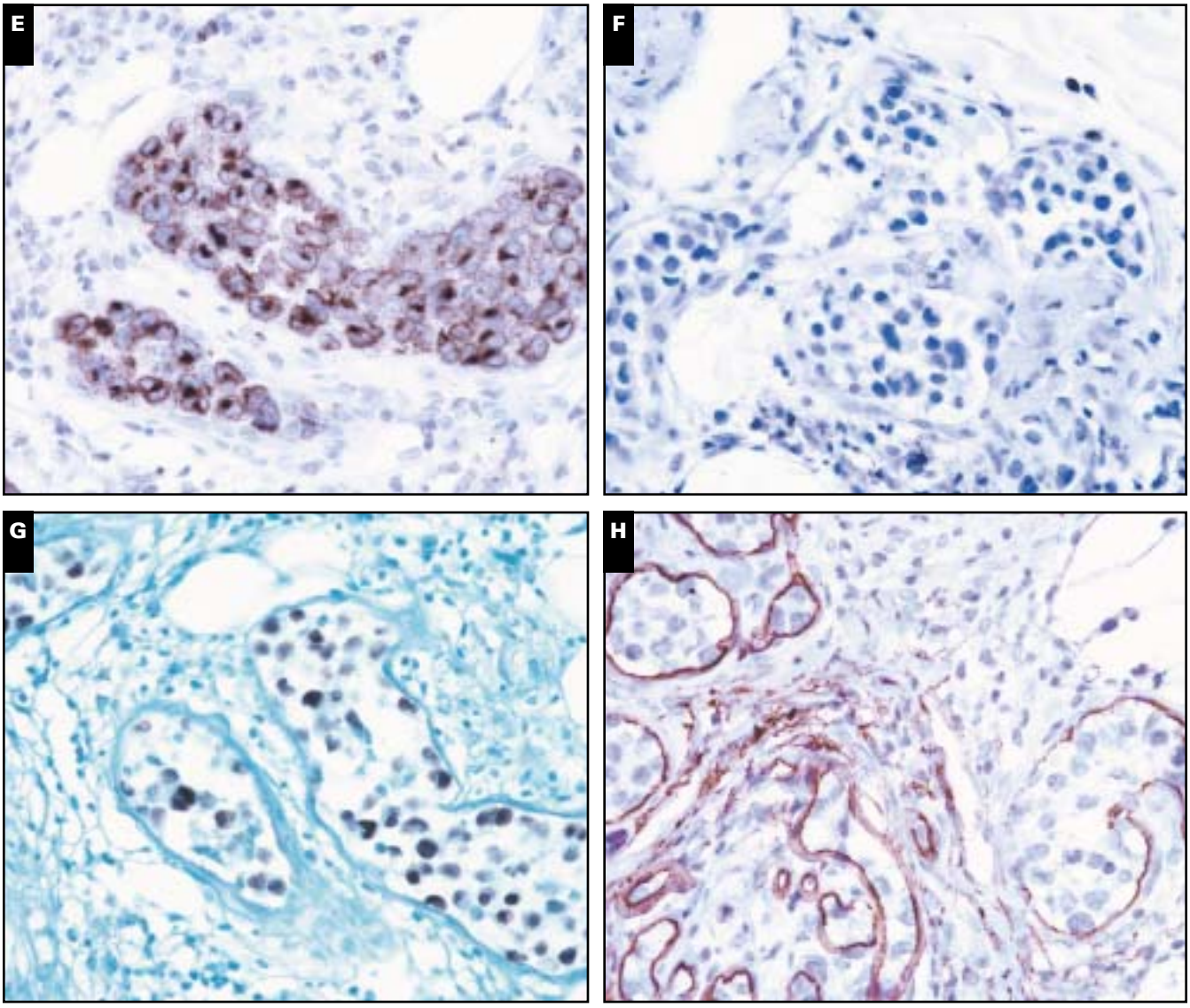

H,The endothelial lining cells of vessels containing tumor cells were reactive for the vascular endothelial cell marker CD34 (immunoperoxidase, hematoxylin counterstain, ×400) but nonreactive for D2-40, a marker for lymphatic endothelial cells (not shown).

small number of cases examined have shown multiple structural abnormalities, with prominent involvement of chromosomes 1, 3, 6, 11, 14, and 18, as noted in other B-cell lymphomas.[37-41] The most common recurrent alterations are –6/6q– (59%) and +18/dup(18q) (41%).

In NK cell neoplasms, a variety of cytogenetic abnormalities have been reported, the most common being del(6)(q21q25) or i(6)(p10)[42] in cases of nasal lymphomas, with the former also noted in aggressive NK cell leukemia. No specific chromosomal aberrations or translocations have been described in the NK cell malignant neoplasms.

The cases described in this report are highly unusual because the tumor cells exhibited the phenotype of a true NK

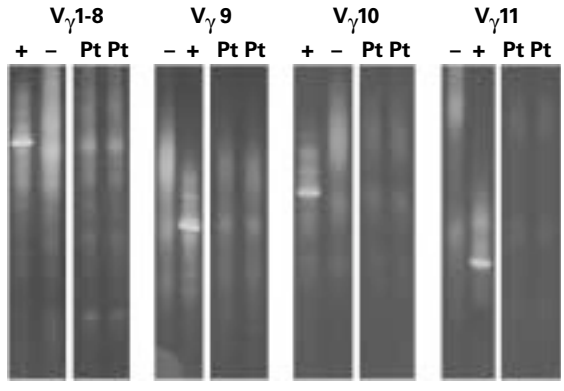

Image 2 (Case 1) Polymerase chain reaction analysis using 4 sets of primers, V_γ1-8, V_γ9, V_γ10, and V_γ11, showed a polyclonal smear with all primer sets. +, positive control; –, negative control; Pt, patient sample.

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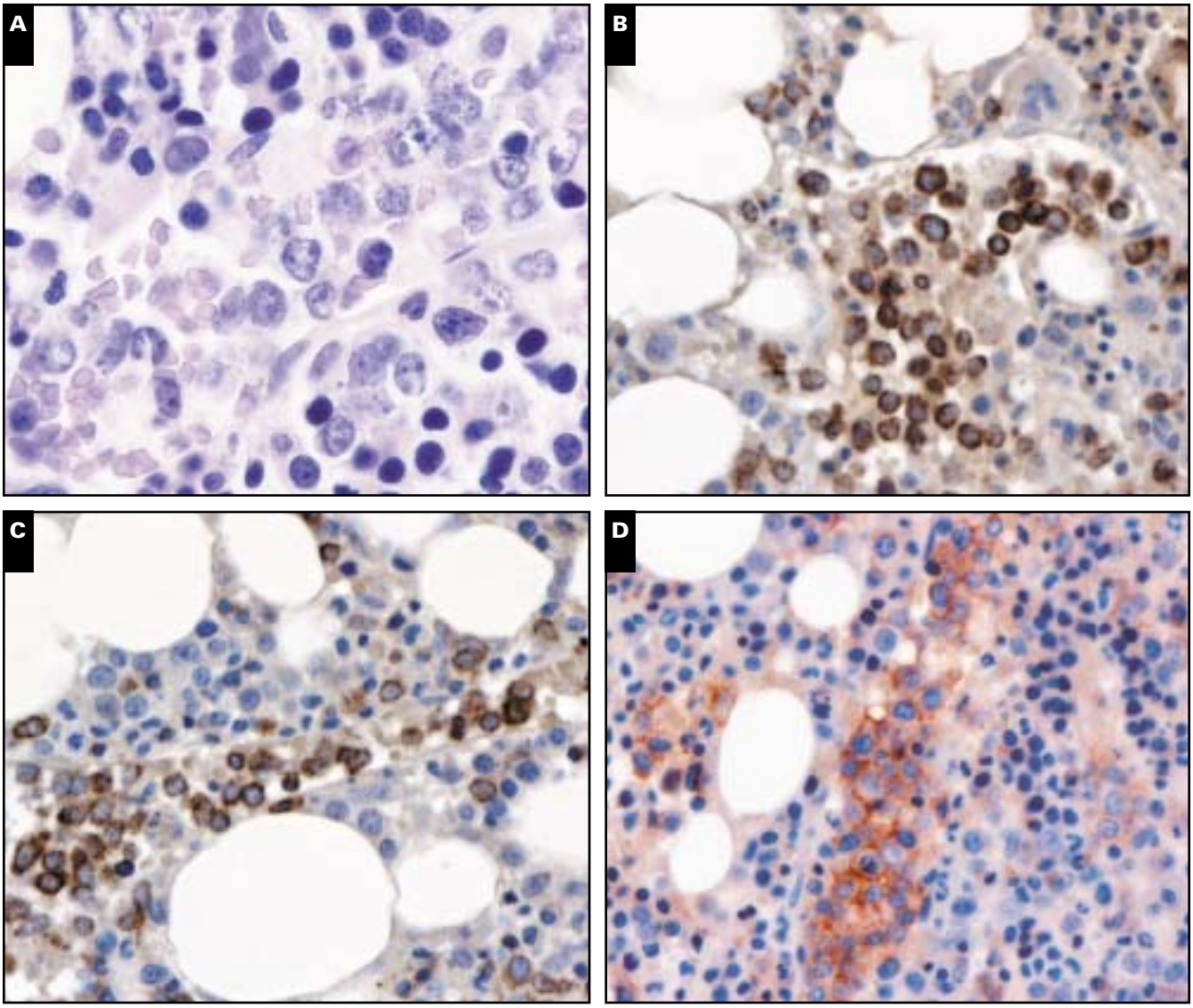

Image 3 (Case 2) Bone marrow biopsy revealed distention of sinusoidal vessels by large atypical tumor cells (**A**, H&E, ×1,000) that exhibited a natural killer cell phenotype and were reactive for CD3ε (**B**), CD7 (**C**), and CD56 (**D**) (**B-D**, immunoperoxidase, hematoxylin counterstain, ×400).

cell. NK cell lymphomas are characterized by tumor cells with an immunophenotype of CD2+, surface CD3–, cytoplasmic CD3ε+, and CD56+, and a germline configuration of the *TCR* gene.[43-45] Tumor cells also expressed cytotoxic granules, including TIA-1, granzyme B, and perforin.

Cases of IVL of definitive NK cell type have not been reported previously, although a case of NK-like IVL has been described. In a recent study, Santucci et al[18] reported a case of IVL affecting a 54-year-man with erythematous plaques on the trunk and thighs. Tumor cells exhibited the following immunophenotype: CD3ε+, CD56+, TIA-1+, granzyme B+, CD30+, MIB-1+, EBER+, EBV latent membrane protein-1–, CD4–, CD8–, CD20–, CD79a–, CD57–, CD68–, and bcl-2–. Findings were regarded as "intravascular NK-like lymphoma" instead of IVL of the NK cell type because no investigation of the TCR status was available. The patient initially had a good response to chemotherapy but died of CNS involvement 17 months after diagnosis. Although this is not a well-documented NK cell IVL, as indicated by the authors, some similarities exist between that case and our cases. However, neoplastic cells were CD30– and bcl-2+ (case 1) in our study.

Recognized variants of NK cell lymphomas include a clinicopathologic spectrum of predominantly extranodal disease, including nasal and extranasal types, aggressive NK cell leukemia/lymphoma, and blastic NK cell lymphoma.[43-46] The extranasal or nasal-type NK cell lymphoma is a counterpart of nasal NK cell lymphoma, occurring in sites other than the nasal cavity and nasopharynx, including skin, upper aerodigestive

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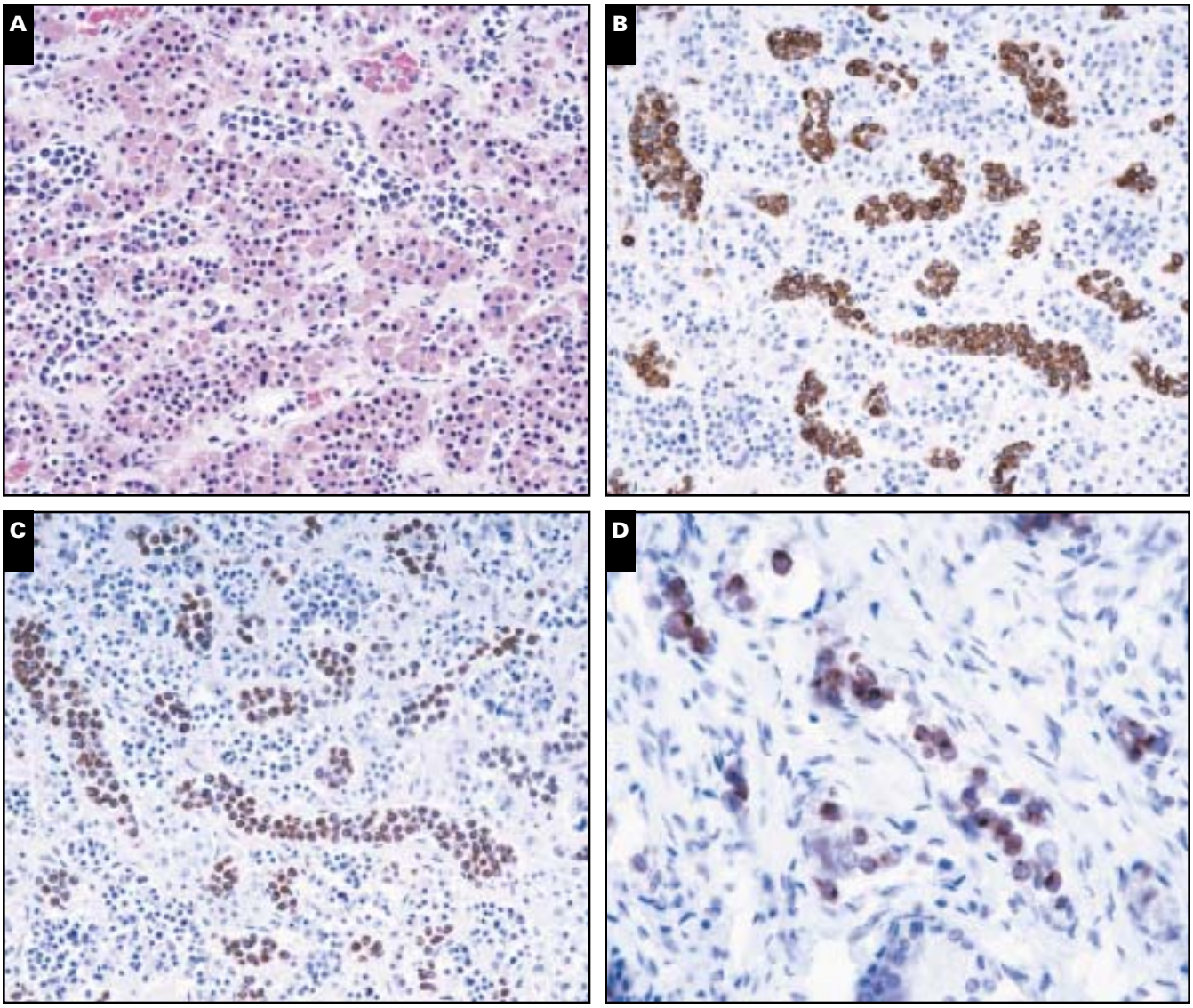

Image 4 (Case 2) Autopsy revealed extensive involvement by intravascular large cell lymphoma of the natural killer (NK) cell type, including the central nervous system. In this section of pituitary, large neoplastic cells distended the vascular lumens (**A**, H&E, ×200) and exhibited an NK cell phenotype, including reactivity for CD7 (**B**) and T-cell intracytoplasmic antigen-1 (TIA-1) (**C**). **D**, Intravascular tumor cells also were reactive for granzyme B as illustrated in a section of cervix (**B-D**, immunoperoxidase, hematoxylin counterstain, ×200).

Table 2
Intravascular Large Cell Lymphoma of the NK Cell Type: Clinical, Immunophenotypic, and Molecular Features

Case No./ Sex/Age (y)	Clinical Features	Immunophenotype of Neoplastic Cells	EBV	Molecular Genetics
1/M/41	Erythematous plaque-like subcutaneous masses of lower extremities; alive with no evidence of disease 1 y after CHOP chemotherapy and stem cell transplantation	CD3ε+, CD2+, CD7+, CD56+, CD43+, TIA-1+, perforin+, bcl-2+; nonreactive for TCRβF1, CD4, CD5, CD8, CD20, CD30, lysozyme, myeloperoxidase, and keratin proteins	+	Germline; TCR studies
2/F/47	Myalgia, arthralgia, weakness, fever, mental signs, confusion, pancytopenia; died of disease 1 mo after onset of symptoms; involved tissues included bone marrow, brain, pituitary, kidney, ovary, and cervix	CD3ε+, CD2+, CD7+, CD56+, TIA-1+, granzyme B+; nonreactive for CD4, CD5, CD8, CD20, and CD57	–	Germline; TCR, IgH studies

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; EBV, Epstein-Barr virus detected by in situ hybridization (EBV-encoded RNA); IgH, immunoglobulin heavy chain; NK, natural killer; TCR, T-cell receptor; TIA-1, T-cell intracytoplasmic antigen-1.

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tract, gastrointestinal tract, testis, spleen, soft tissue, CNS, lung, and liver. Histologically, the infiltrate has a variable cytologic appearance and is associated with angioinvasion, angiocentricity, and zonal necrosis. Similar to nasal NK cell lymphoma, it is almost always associated with EBV and is uniformly fatal, despite initial remissions with radiation and/or chemotherapy.

As noted in the latter group of NK cell neoplasms, EBV positivity was observed in one of our cases (Image 1G). IVLs of the B-cell type are rarely EBV+.[14,17,24] One case of an EBV+ B-cell IVL within Kaposi sarcoma in a patient with AIDS has been reported.[17] Cases of T-cell–type IVL associated with EBV have been described, as detected by in situ hybridization for EBER and/or PCR for the EBV genome.[14] In some cases however, the nonneoplastic lymphocytes and not the tumor cells were positive for EBV. A case of T-cell IVL in Japan associated with human T lymphotropic virus-1 has been described.[47]

The cases described in this report are the first documented examples of IVL in which immunophenotypic and molecular genetic studies support an NK cell phenotype. These cases represent a previously unrecognized variant of IVL and a new lymphoma type within the spectrum of NK cell neoplasms. The prognosis for IVL in general might vary depending on the extent of disease. A high level of clinical suspicion and prompt diagnosis are of prime importance. Patients with limited disease such as skin lesions, as noted in our case 1, or single organ involvement might respond well to chemotherapy. Patients with disseminated disease, particularly those with CNS involvement, have done poorly, as noted in our case 2. Despite the unique phenotype of our cases, the clinical findings seem similar to those described for most cases of IVL, the majority of which are of the B-cell phenotype. Analysis of additional cases with follow-up is required to define further the features of this unusual disorder.

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