Posttransplant Primary Cutaneous Ki-1 (CD30)$^+$/CD56$^+$ Anaplastic Large Cell Lymphoma

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• An anaplastic large cell lymphoma that was negative for Epstein-Barr virus and positive for Ki-1 (CD30) presented as a polypoid scalp mass in a 56-year-old man 16 years after renal transplantation. The lymphoma was of the CD4$^+$ cytotoxic T-cell lineage, and the tumor cells also expressed CD56. Despite reduction in the dose of immunosuppression and localized radiotherapy, the tumor had rapidly progressed to involve the soft tissue of the right hand. Systemic chemotherapy induced complete regression of the soft tissue lesion. This case illustrates that posttransplant primary cutaneous CD30$^+$ anaplastic large cell lymphomas may assume an aggressive clinical course but can still be controlled by systemic chemotherapy.

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Posttransplant lymphoproliferative disorders (PTLDs) are among the most common complications of transplantation, and most of these are Epstein-Barr virus (EBV)–related high-grade B-cell lymphomas. Although extranodal presentation is one of the characteristic features of a PTLD, primary cutaneous lymphomas in organ recipients are rare, and only about 30 cases have been reported.[1] Posttransplant primary cutaneous T-cell lymphomas are even rarer and therefore can cause diagnostic difficulties for both pathologists and clinicians. Because of a limited number of reported cases,[2–12] the biologic behavior of these lymphomas has not been fully characterized. Here, we describe a case of EBV-negative primary cutaneous CD30$^+$/CD56$^+$ anaplastic large cell lymphoma (ALCL) of the CD4$^+$ cytotoxic T-cell lineage that occurred in a 56-year-old renal transplant recipient. We also review published reports of these lesions.

REPORT OF A CASE

A 56-year-old Korean man presented with a polypoid mass on his forehead. The patient had been on hemodialysis because of chronic renal failure and had undergone kidney transplantation 16 years ago. Since that time, his immune system had been suppressed with prednisolone, azathioprine, and cyclosporine. Physical examination revealed a 4 × 3-cm relatively well-demarcated polypoid mass on the forehead surrounded by erythematous skin (Figure 1). Laboratory analyses at presentation revealed a slightly increased erythrocyte sedimentation rate (31 mm at the first hour) and moderate normochromic normocytic anemia with a hemoglobin concentration of 9 g/dL and a mean corpuscular volume of 93 μm^3. The white blood cell count was 7.9 × $10^3/\mu L$, with 14% lymphocytes, 83% neutrophils, and 3% monocytes; the platelet count was 242 × $10^3/\mu L$. An excisional biopsy of the forehead mass was diagnosed as stage IE cutaneous T-cell lymphoma, and the patient was treated with radiation therapy (5000 rad for 4 weeks) after reduction of the dose of the immunosuppressive therapy. Five weeks after completion of the radiation therapy, the lymphoma relapsed on the thenar and adductor pollicis muscle of the right hand, and bone marrow involvement of the first metacarpal bone was also noted. Cytologic examination of the fine-needle aspiration biopsy of the thenar muscle of the right hand revealed atypical cells similar to those in the forehead mass. Combination chemotherapy with cyclophosphamide, adriamycin, vincristine, and prednisolone was employed, and after two cycles, the intramuscular lymphoma disappeared. The patient has been in a state of complete remission for 6 months after the completion of 6 cycles of chemotherapy.

PATHOLOGIC FINDINGS

Histologic examination of the biopsy specimen from the forehead revealed diffuse nonepidermotropic infiltrates with cohesive sheets of large pleomorphic tumor cells (Figure 2, a). The tumor cells had abundant amphophilic cytoplasm and vesicular nuclei with prominent eosinophilic nucleoli (Figure 2, b). The cellular infiltrates involved the dermis and subcutaneous fat. Mitoses, including atypical forms, were commonly observed, and multinucleated tumor giant cells were present. Immunohistochemical evaluation of paraffin-embedded tissue sections demonstrated that most of the tumor cells were positive for the T-lineage antigens CD45RO (UCHL-1), CD3, CD4, and CD5. The tumor cells had diffuse and strong membrane and Golgi pattern staining for CD30 (Ki-1) (Figure 3, a). CD56 and cytotoxic molecules (T-cell intracellular antigen and granzyme B) were also strongly expressed in the majority of tumor cells (Figure 3, b and c). A clonal T-cell receptor γ gene rearrangement was detected by means of a polymerase chain reaction assay of DNA extracted and amplified from formalin-fixed, paraffin-embedded tissue, as previously described.[13] Latent membrane proteins of EBV and human herpesvirus 8 were not demonstrated by immunohistochemical staining, and in situ hybridization for EBV-encoded RNA mRNA produced a negative result.

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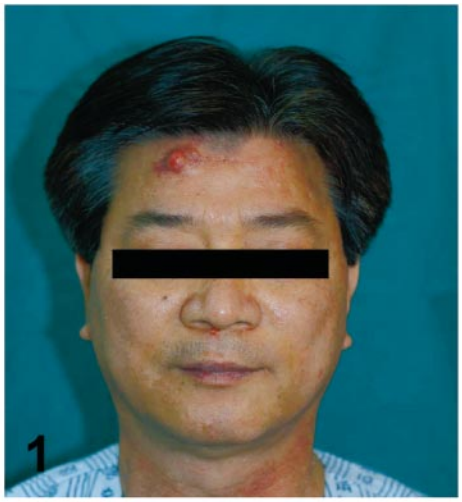

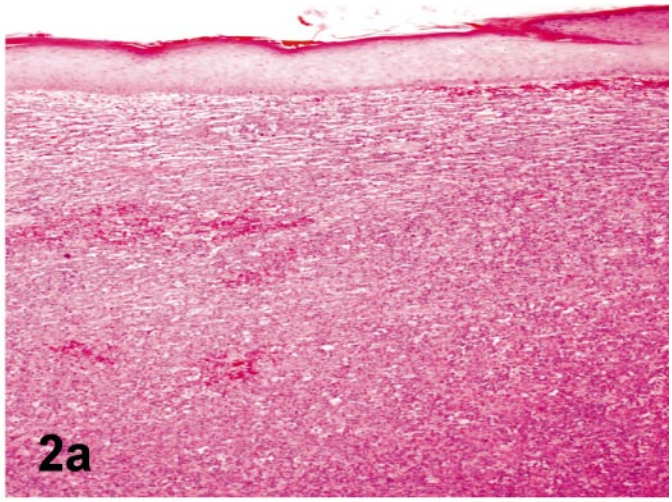

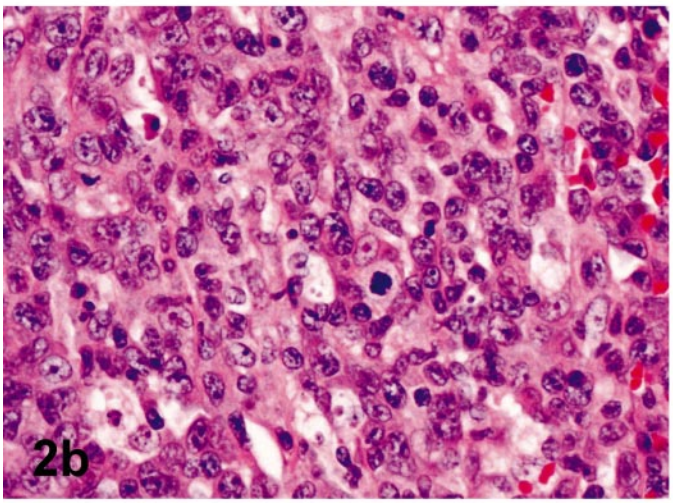

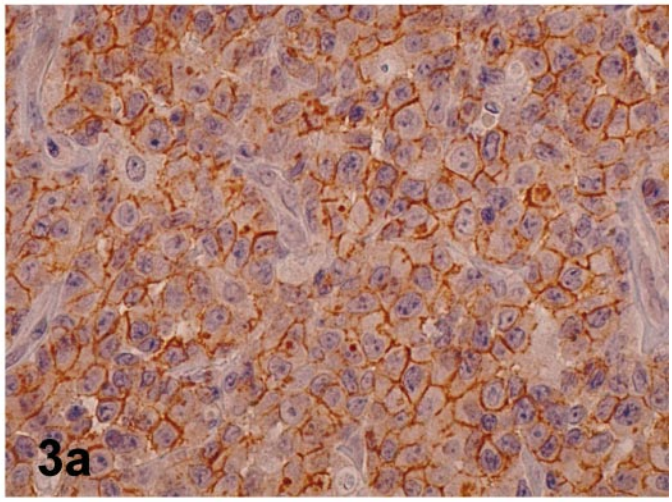

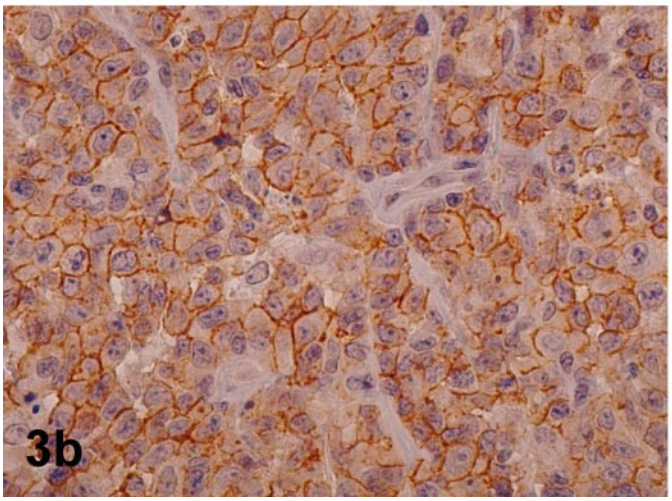

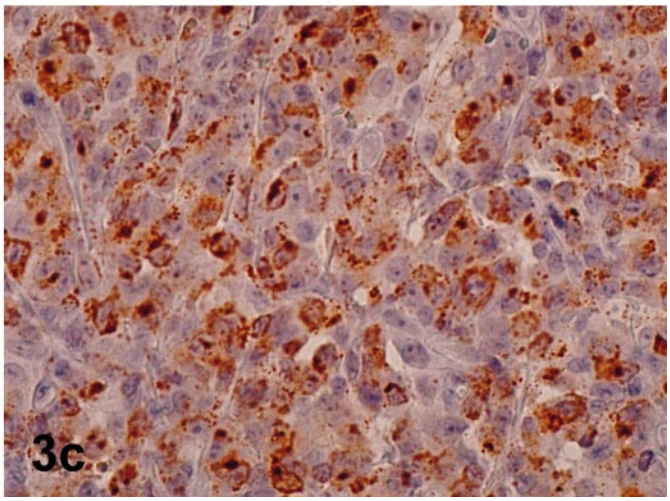

Figure 1. *A relatively well-demarcated polypoid mass, 4 × 3 cm, on the forehead of a 56-year-old renal transplant recipient.*

Figure 2. *Microscopic appearance of the tumor. a, Dense, diffuse, nonepidermotropic cellular infiltrates composed of large and atypical lymphocytes throughout the reticular dermis. b, Tumor cells with round, oval, or irregular nuclei, a large prominent eosinophilic nucleolus, and occasional mitotic figures (hematoxylin-eosin, original magnifications ×40 [a] and ×400 [b]).*

Figure 3. *Immunohistochemical stains. a, CD30 reveals membranous and Golgi pattern (original magnification ×400). b, CD56 staining reveals cell membrane pattern (original magnification ×400). c, Granzyme B staining reveals cytoplasmic granular pattern (original magnification ×400).*

Characteristics of Reported Cases of Posttransplant Cutaneous T-Cell Lymphoma*						
Type	Age, y/Sex	Allograft Organ	Interval	Clinical Outcome	Epstein-Barr Virus	Source, y
MF	52/M	Kidney	4 y	Deceased	NR	Pascual et al,[2] 1992
MF	53/M	Kidney	1.5 y	Remission	NR	Pascual et al,[2] 1992
MF	52/F	Kidney	7 y	Remission	−	Defossez-Tribout et al,[3] 2003
MF	65/M	Heart	4 mo	Deceased	NR	McMullan et al,[4] 2001
Sezary syndrome	57/M	Kidney	11 y	Deceased	−	Euvrard et al,[5] 1992
Non-MF T-cell lymphoma	NR	Kidney	NR	Deceased	−	McGregor et al,[6] 1993
Non-MF T-cell lymphoma	58/M	Kidney	6 y	Remission	+	Lye,[7] 2000
Cutaneous T-cell lymphoma	64/F	Kidney	5 y	Deceased	−	Ward et al,[8] 2002
Subcutaneous panniculitis-like T-cell lymphoma	55/F	Kidney	5 y	Deceased	−	Kaplan et al,[9] 1993
ATLL	43/M	Kidney	NR	Deceased	−	Hoshida et al,[10] 2001
CD30+ ALCL	51/F	Kidney	10 mo	Remission	−	Seçkin et al,[11] 2001
CD30+ ALCL	60/M	Kidney	5 y	Deceased	−	Cooper et al,[12] 2003
CD30+ ALCL	56/M	Kidney	16 y	Remission	−	Present case

* MF indicates mycosis fungoides; ATLL, adult T-cell lymphoma/leukemia; ALCL, anaplastic large cell lymphoma; and NR, not reported.

COMMENT

Recipients of organ transplants are at an increased risk of secondary malignancies. There is a remarkable difference in the incidence of various posttransplant malignancies in eastern and western countries; a lower frequency of skin cancer in eastern countries and a higher frequency of renal and thyroid cancers in western countries have been noted.[14] However, non-Hodgkin lymphoma is one of the most common posttransplant malignancies regardless of country of origin. The majority of posttransplant lymphomas are high-grade B-cell non-Hodgkin lymphomas with a close association to EBV and a high incidence of extranodal presentation. T-cell neoplasms make up a high proportion of posttransplant lymphomas, especially in Japan.[10] Most posttransplant T-cell lymphomas are also of high grade and, like posttransplant B-cell lymphomas, are commonly extranodal in presentation, but they are usually EBV negative. The central nervous system and gastrointestinal tract are common extranodal sites for PTLDs, but posttransplant primary cutaneous lymphomas are rare, and fewer than 30 cases have so far been reported.[1] Among them, 12 cases have been T-cell lymphomas, and the distribution of morphologic types of primary cutaneous T-cell lymphomas is similar regardless of the immune status of the patients (Table).

The clinical presentation, morphologic features, immunophenotypes, and genetic features of the present case satisfy the criteria for the diagnosis of primary cutaneous CD30+ ALCL. A T-cell receptor γ gene rearrangement was found and CD3, CD4, CD5, T-cell intracellular antigen, and granzyme B were expressed in the tumor cells. These results confirm the CD4+ cytotoxic T-cell lineage of the tumor cells, which is the most common and characteristic immunophenotype of primary cutaneous CD30+ ALCL. There have been only 2 previous case reports of posttransplant primary cutaneous CD30+ large cell lymphoma. The first case[11] occurred only 10 months after renal transplantation in a 51-year-old woman, and she had 4 cutaneous lymphoma relapses within 1 year in different regions of her body. However, the primary and relapsed tumors were all cured by localized radiotherapy, and there was no systemic spread of the tumor. The second report[12] was of a 60-year-old man with multinodular skin lesions 66 months after renal transplantation. Local radiotherapy was employed after an unsuccessful attempt to induce tumor regression by reducing the dosage of the immunosuppression drugs. The tumor nodules initially responded to the local radiotherapy, but a few months later there was recurrence of skin tumors with regional lymph node metastasis and suspicious liver and kidney involvement. The patient died of cardiac failure 18 months after the original diagnosis of skin lymphoma. The cardiac failure probably was due to myocardial involvement by the lymphoma, although initially the patient demonstrated a favorable response to systemic chemotherapy. Unusual findings of the present case were a long interval after the transplantation before the appearance of the tumor, the strong expression of CD56 by the tumor cells, and an initial aggressive clinical course of the skin tumor to involve extracutaneous organs despite the radiotherapy and reduction of the immunosuppression dosage. Contrary to classical PTLDs, which are EBV-associated B-cell proliferations characterized by early onset, aggressive behavior, tropism for extranodal sites, and a tendency to regression after reduction or withdrawal of immunosuppressive therapy, T-cell malignancies observed in allograft patients are not easily proven to be related to transplantation. Even in B-cell PTLDs, late occurring disorders seem to be an entity distinct from classical early onset PTLDs because they are frequently EBV negative and invariably clonal and are associated with a poorer outcome than are early-onset types.[15] Similar to late occurring B-cell PTLDs, T-cell PTLDs can occur a long time after transplantation (average interval of 6.3 years, with a range of <1 month to 28 years) and are associated with low incidence of EBV infection and an aggressive clinical course. Review of the reported cases of posttransplant primary cutaneous T-cell lymphomas also revealed low frequency of EBV infection and a long lag time with a relatively aggressive clinical course as for systemic T-cell PTLDs. The distribution of morphologic types of posttransplant primary cutaneous T-cell lymphomas is similar, regardless of the immune status of the patient. The exact causal relationship between transplantation and the reported cases of posttransplant cutaneous T-cell lymphoma, including the present case, is not known, and further analyses with a large number of cases are needed to establish the relationship.

Although CD56 has been used to define natural killer cell neoplasms, CD56 is also expressed in a high proportion (18%) of systemic CD30+ T/null-cell type ALCL. CD56+ systemic ALCL have a high incidence of bone involvement and a significantly poor prognosis overall.[16] To

our knowledge, there have been no studies analyzing the expression of CD56 in primary cutaneous CD30+ ALCL. Eight cases of lymphomatoid papulosis, which has an immunophenotype identical to that of CD30+ primary cutaneous ALCL, were reported negative for CD56.[17] However, there has been a recent case report of a CD56+ primary cutaneous CD30+ ALCL.[18] In contrast to the excellent prognosis of CD30+ primary cutaneous ALCL, the CD56+ case did not respond to an intensive chemotherapy regimen, and the authors suggested that CD56 expression may be a poor prognostic factor. The present CD56+ ALCL had an initial aggressive clinical course, with involvement of distant soft tissue shortly after the radiation therapy, but the soft tissue mass completely regressed after systemic chemotherapy. Considering the initial aggressive clinical course of this case, coexpression of CD56 might be considered an underlying pathogenic mechanism of aggressive biologic behavior. However, the present case was also associated with long-standing immunosuppression, and approximately 10% of immunocompetent patients with cutaneous ALCL develop disseminated and clinically aggressive disease.[19] CD56 expression and immunosuppression as prognostic factors in primary cutaneous ALCL must be analyzed with a large number of cases, as has been done with systemic ALCL.

The underlying pathogenic mechanism of posttransplant cutaneous T-cell lymphoma is unknown. In contrast to posttransplant B-cell non-Hodgkin lymphomas, the EBV genome was detected in only 1 case of posttransplant cutaneous T-cell lymphoma, and there has been 1 Japanese case of posttransplant cutaneous T-cell lymphoma associated with human T-cell leukemia virus 1.[10] These findings suggest that most posttransplant cutaneous T-cell lymphomas are not associated with oncogenic viruses. Although reduced immune surveillance, chronic antigenic stimulation by the graft, and direct oncogenic potential of immunosuppressive drugs have been suggested as underlying risk factors for posttransplant T-cell lymphomas, it is necessary to determine whether posttransplant cutaneous T-cell lymphomas are coincidental or have a causative relationship with immunosuppressive therapy.

We have described the pathologic and clinical findings of a primary cutaneous ALCL diagnosed 16 years after renal transplantation. Although the exact causal relationship between transplantation and the tumor is not known, this case illustrates that primary cutaneous CD56+ ALCL that occurs as a late complication in the transplant recipient demonstrates an aggressive clinical course that can be controlled by systemic chemotherapy.

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References

1. Euvrard S, Kanitakis J, Claudy A. Neoplastic skin diseases in organ transplant recipients. *Am J Cancer.* 2002;1:109–120.
2. Pascual J, Torrelo A, Teruel JL, Bellas C, Marcen R, Ortuno J. Cutaneous T-cell lymphomas after renal transplantation. *Transplantation.* 1992;53:1143–1145.
3. Defossez-Tribout C, Carmi E, Lok C, Westeel PF, Chatelain D, Denoueux JP. Cutaneous T-cell lymphoma following renal transplantation. *Ann Dermatol Venereol.* 2003;130:47.
4. McMullan DM, Radovaneevic B, Jackow CM, Frazier OH, Duvic M. Cutaneous T-cell lymphoma in a cardiac transplant recipient. *Tex Heart Inst J.* 2001; 28:203–207.
5. Euvrard S, Noble CP, Kanitakis J, et al. Brief report: successive occurrence of T-cell lymphomas after renal transplantation in a patient with multiple cutaneous squamous cell carcinomas. *N Engl J Med.* 1992;327:1924–1926.
6. McGregor JM, Yu CCW, Lu QL, Cotter FE, Levison DA, MacDonald DM. Posttransplant cutaneous lymphoma. *J Am Acad Dermatol.* 1993;29:549–554.
7. Lye WC. Successful treatment of Epstein-Barr virus–associated T-cell cutaneous lymphoma in a renal allograft recipient: case report and review of the literature. *Transplantation.* 2000;32:1988–1989.
8. Ward HA, Russo GG, McBurney E, Millikan LE, Boh EE. Posttransplant primary cutaneous T-cell lymphoma. *J Am Acad Dermatol.* 2002;44:675–680.
9. Kaplan MA, Jacobson JO, Ferry JA, Harris NL. T-cell lymphoma of the vulva in a renal allograft recipient with associated hemophagocytosis. *Am J Surg Pathol.* 1993;17:842–849.
10. Hoshida Y, Li T, Dong Z, et al. Lymphoproliferative disorders in renal transplant patients in Japan. *Int J Cancer.* 2001;91:869–875.
11. Seçkin DS, Demirhan B, Oğuz Güleç T, Arikan Ü, Haberal M. Posttransplantation primary cutaneous CD30 (Ki-1)-positive large-cell lymphoma. *J Am Acad Dermatol.* 2001;45:S197–S199.
12. Cooper SM, Turner GDH, Hollowood K, et al. Primary cutaneous large cell CD30+ lymphoma in a renal transplant recipient. *Br J Dermatol.* 2003;149: 426–428.
13. Choi JS, Nam DH, Ko YH, et al. Primary central nervous system lymphoma in Korea: comparison of B- and T-cell lymphomas. *Am J Surg Pathol.* 2003;27: 919–928.
14. Hoshida Y, Tsukuma H, Yasunaga Y, et al. Cancer risk after renal transplantation in Japan. *Int J Cancer.* 1997;71:517–520.
15. Lebland V, Davi F, Charlotte F, et al. Posttransplant lymphoproliferative disorders not associated with Epstein-Barr virus: a distinct entity? *J Clin Oncol.* 1998;16:2052–2059.
16. Suzuki R, Kagami Y, Takeuchi K, et al. Prognostic significance of CD56 expression for ALK-positive and ALK-negative anaplastic large-cell lymphoma of T/null cell phenotype. *Blood.* 2000;96:2993–3000.
17. Harvell J, Vaseghi M, Natkunam Y, Kohler S, Kim Y. Large atypical cells of lymphomatoid papulosis are CD56-negative: a study of 10 cases. *J Cutan Pathol.* 2002;29:88–92.
18. Chang SE, Park IJ, Huh J, et al. CD56 expression in a case of primary cutaneous CD30+ anaplastic large cell lymphoma. *Br J Dermatol.* 2000;142: 766–770.
19. Bekkenk MW, Geelen FAMJ, Voorst Vader PC, et al. Primary and secondary cutaneous CD30+ lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Study Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. *Blood.* 2000;95:3653–3661.