A 56-year-old woman was admitted to this hospital because of fever, rash, and lymphadenopathy. Eleven weeks earlier, fever and a diffuse maculopapular skin rash had developed shortly after she was stung by an ant. Her symptoms responded to corticosteroids, but 6 weeks before admission, lymphadenopathy developed, followed by recurrent fever and rash. Evaluation disclosed no evidence of infection, and specimens from lymph-node biopsies performed on two occasions did not yield a diagnosis. A diagnostic procedure was performed.

Clinical Pearls

- **Neoplastic Causes of Lymphadenopathy**
  After most non-neoplastic causes of lymphadenopathy are ruled out, lymphoma must be considered in the patient in this case vignette. Most lymphomas present subacutely over weeks to months, in contrast to the abrupt onset described in this case. The majority of non-Hodgkin's lymphomas are of B-cell origin, and the diagnosis is typically straightforward on examination of an excisional biopsy specimen from an involved lymph node. Fever, lymphadenopathy, and splenomegaly may be seen in many lymphomas, but a diffuse rash is not a common feature.

- **Angioimmunoblastic T-Cell Lymphoma**
  Angioimmunoblastic T-cell lymphoma (AITL) is the second most common peripheral T-cell lymphoma. Unlike other non-Hodgkin's lymphomas, this disease characteristically presents acutely with diffuse lymphadenopathy and fever, mimicking an infectious disease, and the presence of a diffuse, pruritic, maculopapular rash. The swollen lymph nodes are in the size range seen in inflammatory or infectious processes, as in the case described. The rash and lymphadenopathy may wax and wane, as they did in this case, providing the misleading impression that the patient has responded to antibiotics or has a resolving inflammatory process. Splenomegaly is present in just over half of patients with AITL. Up to 80% of patients have polyclonal hypergammaglobulinemia, which contributed to the original description of AITL as “angioimmunoblastic lymphadenopathy with dysproteinemia.” In up to half of patients, a diagnosis of AITL is not made on examination of the initial biopsy specimens. Serial biopsies may be necessary to show the evolution of a recognizably malignant process.

Morning Report Questions

**Q**: What are the treatment options for angioimmunoblastic T-cell lymphoma?

**A**: It is challenging to treat a patient with angioimmunoblastic T-cell lymphoma (AITL). Like many other peripheral T-cell lymphomas, the disease has a poor prognosis, with a median overall survival of less than 3 years. Combination chemotherapy achieves a complete response in 50 to 70% of patients, but less than 30% remain disease free. High-dose chemotherapy with autologous stem-
cell support has been reported to result in long-term survival in more than half of patients. Favorable results have also been reported with allogeneic stem-cell transplantation, but this procedure is associated with a high risk of graft-versus-host disease and death. New therapies under investigation in AITL and other peripheral T-cell lymphomas include the anti-CD52 monoclonal antibody alemtuzumab, denileukin diftitox (interleukin-2 bound to diphtheria toxin), the proteosome inhibitor bortezomib, histone deacetylase inhibitors, new antifolate molecules, monoclonal antibodies against T cells with specificity for certain epitopes, and antiangiogenic therapy.

Q: What lymphomas evade identification on routine biopsy?

A: Hodgkin's lymphoma may present with diffuse lymphadenopathy and constitutional symptoms; malignant Reed–Sternberg cells, though rare, are pathognomonic. T-cell/histiocyte-rich large-B-cell lymphoma is an uncommon variant of diffuse large-B-cell lymphoma that usually presents at an advanced stage with fever and constitutional symptoms; lymph node biopsies characteristically reveal a minority of malignant cells in a background rich in nonmalignant and inflammatory cells. These histologic features make the diagnosis of both diseases difficult when fine-needle aspiration biopsy and core biopsy are used. Peripheral T-cell lymphomas also present unique diagnostic challenges. Unlike in B-cell lymphomas, distinguishing between reactive and neoplastic T cells is often not possible with the use of morphologic and immunophenotypic techniques alone in peripheral T-cell lymphomas. The diagnosis often requires analysis of T-cell receptor genes for clonal rearrangements.

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