Diagnostic and Therapeutic Challenges of Primary Cutaneous Lymphomas

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Primary cutaneous lymphomas represent a broad spectrum of distinct entities with multiple clinical and pathologic presentations, prognosis, and treatment approaches. Given their rarity and heterogeneity, these entities represent diagnostic and therapeutic challenges, thus requiring a multidisciplinary approach and expertise to ensure appropriate diagnosis and management. According to the new World Health Organization (WHO) classification, primary cutaneous CD30-positive lymphoproliferative disorders (CD30+ LPD) are the second most common group of cutaneous T-cell lymphomas, accounting for approximately 30% of all cases.[1] This group includes primary cutaneous anaplastic large-cell lymphoma (ALCL), lymphomatoid papulosis (LyP), and borderline cases.

In this issue of ONCOLOGY, the article by Marshall Kadin focuses on clinical and pathologic features, and particularly on the management of CD30+ LPD. I would like to emphasize several important points from his article.

Diagnostic Considerations

The use of the term CD30+ LPD in the initial clinical and pathologic assessment is preferable over LyP or ALCL, because of overlapping clinical, histologic, and immunophenotypical characteristics. At one end of the spectrum, LyP is defined as a chronic, recurrent, self-healing papulonecrotic or papulonodular skin disease with histologic features suggestive of CD30+ malignant lymphoma. At the opposite end of the spectrum, primary cutaneous ALCL is a lymphoma composed of large cells with an anaplastic, pleomorphic, or immunoblastic cytomorphology and expression of CD30 antigen by the majority of the tumor cells. In contrast to systemic ALCL, primary cutaneous ALCLs rarely carry the t(2;5) translocation and are usually anaplastic large-cell lymphoma kinase protein (ALK-1)-negative.[2]

As Kadin points out, primary cutaneous CD30+ LPDs have a favorable prognosis with a 10-year survival exceeding 90% in most patients.[3] Patients presenting with multifocal skin lesions and/or regional lymph nodes have prognoses similar to those of patients with skin lesions only. Many clinicians, however, are unaware of the spectrum of CD30+ LPD, and patients have been misdiagnosed or treated with unnecessarily aggressive treatment regimens.[3] Patients with LyP are often inappropriately treated with multiagent chemotherapy. The diagnosis of CD30+ LPD requires the exclusion of other cutaneous infiltrates characterized by CD30 expression, which were recently reviewed by Werner et al.[4] These conditions include reactive and neoplastic diseases such as arthropod bites, scabies, pityriasis lichenoides, Langerhans cell histiocytosis, cutaneous B-cell lymphomas with immunoblastic or large-cell features, CD30+ large-cell transformation of mycosis fungoides, CD30+ cutaneous NK/T-cell lymphoma, and secondary cutaneous involvement of systemic ALCL. Therefore, clinical exclusion of these conditions is essential before establishing a diagnosis of CD30+ LPD and to avoid unnecessary aggressive therapy.

Risk of Malignancy

The literature shows that patients with LyP have a 10% to 20% increased risk for developing lymphoid malignancy. Risk factors that could identify patients most likely to develop malignancy are not known. In the study by Wang et al, LyP patients and matched controls were also examined to
estimate risk of malignancy compared to expectations of known Surveillance, Epidemiology, and End Results (SEER) data.[5] Interestingly, this study found an increased risk of both lymphoid and nonlymphoid malignancies in the LyP population. A recently published retrospective study of 84 patients with LyP from M.D. Anderson Cancer Center found a 40% incidence of prior, coexisting, or subsequently developed lymphoma.[6] Patients with LyP had a higher association with a coexisting lymphoid malignancy than had been seen in most previous reports. These results confirm similar observations from another cutaneous lymphoma referral center at Stanford.[7]

Patients diagnosed with LyP at a younger age tend to be at higher risk for malignant transformation, underlining the importance of long-term follow-up. What causes the malignant transformation? Kadin et al suggested that a mutation in the transforming growth factor–beta receptor gene may be responsible for escape from growth regulation and progression to lymphoma.[8]

Treatment Strategies

How should we use current treatment options when initiating therapy and when should we escalate treatment? Kadin includes an impressive review of treatment strategies for patients with CD30+LPD. In summary, there is no curative treatment available. As highlighted in this article, treatment of LyP is not known to alter the natural history of the disease or the risk of developing associated malignancies. There is no role for multiagent systemic chemotherapies. Many patients do not require treatment if their disease is asymptomatic, especially given the possibility of spontaneous resolution of lesions. Observation in patients with few lesions is recommended, whereas in patients with more disseminated disease, low-dose methotrexate or ultraviolet (UV) light therapy is effective in clearing disease. In contrast, localized radiation therapy for solitary or localized lesions is the preferred treatment for cutaneous ALCL, with methotrexate or systemic chemotherapy reserved for cases with high tumor burden and/or extracutaneous involvement.

In the past several years, experimental immunotherapies have emerged. Notably, CD30 is an attractive molecule for targeted therapy. Recently published results of a phase II trial with the monoclonal antibody SGN-30 in heavily pretreated patients with cutaneous ALCL, LyP, and transformed mycosis fungoides demonstrated promising results, with low toxicities reported.[9] SGN-30 was given at an escalating dose of 4 mg up to 12 mg per kg every 3 weeks, with a 70% overall response rate (complete and partial responses) observed.

Conclusion

In conclusion, the article by Marshall Kadin nicely summarizes the current concepts and treatment strategies in CD30+ LPD. It is important to know that observation vs first-line treatment with low-dose methotrexate or UV light therapy is indicated in patients with LyP. However, long-term follow-up is required, as 10% to 20% of patients develop a secondary malignancy. Treatment of choice in patients with primary cutaneous ALCL should rely on the extent of skin and/or extracutaneous disease. Aggressive, multiagent chemotherapy is rarely indicated. Novel therapies that target CD30 expression and associated signaling pathways are on the way.

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