New Insights, Future Directions in Primary Cutaneous Lymphoproliferative Disorders

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The spectrum of CD30+ lymphoproliferative diseases of the skin includes CD30+ cutaneous anaplastic large cell lymphoma, lymphomatoid papulosis, as well as borderline cases. These entities constitute the second most common group of cutaneous lymphomas according to the newly revised World Health Organization and European Organisation for Research and Treatment of Cancer consensus classification. Recent progress in immune and molecular biology, and identification of therapeutic targets have increased our understanding of these diseases and have led to novel treatment approaches. This review will provide an update on recent findings of immunologic, molecular, cytogenetic features and treatment strategies for patients with CD30+ lympho-proliferative diseases.

Not all T-cell lymphomas are alike. Recently, attention in the lymphoma community has been focused on further understanding the biologic aspects of the different T-cell lymphomas. Though histologically similar to its systemic counterparts, primary cutaneous lymphoma differs in clinical behavior, prognosis, and treatment approaches. Of these, the primary cutaneous CD30+ lymphoproliferative disorders (PCLPD) are the focus of the discussion by Querfeld et al. Their article particularly emphasizes the biologic characteristics that render these diseases clinically challenging. I would like to highlight a few important points from the article.

Challenges in Diagnosis

The PCLPDs make up a diagnostically challenging yet clinically favorable prognostic group of cutaneous lymphomas. The classification includes lymphomatoid papulosis (LyP), cutaneous anaplastic large-cell lymphoma (CALCL), and borderline cases that share characteristics of the two entities but do not classically belong in either category.[1] Expression of the CD30 antigen unites this group phenotypically, though CD30 expression is not unique to these entities. Categorization is further complicated by biologic heterogeneity through limitations in our current diagnostic testing and criteria. The Querfeld article includes a review table of the histologic subtypes of LyP. The LyP histologic resemblance to malignant lymphoproliferative disorders includes type A and Hodgkin's lymphoma, type B and mycosis fungoides (MF), and type C and anaplastic large-cell lymphoma (ALCL). There is also controversy regarding the clonality of LyP, though this may be explained by differences in technique,[2] according to some authors. These variables in combination with the rarity of these diseases can lead to diagnostic challenges.

The differential diagnosis for a CD30+ cutaneous lesion is not limited to PCLPDs. In the instance of ALCL, staging is crucial to ensure the diagnosis is primary cutaneous ALCL rather than secondary cutaneous involvement of systemic ALCL. This distinction is far from arbitrary. The article by Querfeld et al reviews cytogenetic and other factors that may account for differences in clinical behavior. Additionally, other infectious, oncologic, and inflammatory entities can present as CD30+ lesions, which are recently reviewed by Kempf et al.[3] The spectrum of CD30+ expression ranges from MF transformed to high-grade large-cell lymphoma.[4] Although consensus on treating large-cell transformation of MF has not been reached, the prognosis for this entity differs significantly from the PCLPDs. Therefore, distinguishing these disorders accurately is paramount to appropriate management. These examples underscore the importance of correlation between clinical presentation and appearance of lesions with their histopathologic findings in the diagnosis of cutaneous lymphomas.

PCLPDs and Systemic Cancer Risk

In the setting of PCLPD, systemic surveillance is important as a significant number of patients will have extracutaneous manifestations of ALCL, or in the case of LyP patients, additional malignancies.
In an effort to quantify risk according to systemic progression, data from the Dutch registry for cutaneous lymphomas examined this question. In this series of 79 patients with primary CALCL, only 10% went on to develop extracutaneous disease. Also, 118 LyP patients were studied, and 23 (19%) had associated lymphomas before, during, or after development of LyP. These lymphomas included systemic CD30+ ALCL, MF, and Hodgkin's lymphoma.[5]

The increased risk of lymphomas in patients with LyP has been reported previously[6-8] and ranges from 10% to 20%,[7,8] with one series reporting an 80% cumulative risk over time.[6] LyP patients and matched controls were also examined, in another study, to estimate risk of malignancy compared to expectations of known Surveillance, Epidemiology, and End Results (SEER) data. This study found an increased risk of both lymphoid and nonlymphoid malignancies in the LyP population. The investigators postulate the role of genetic instability in these patients as a possible explanation for their findings.[9]

None of the above studies linked LyP histology subclassifications with risk of secondary malignancy. Currently, there has been no correlation between particular LyP subtypes and transformation to specific systemic lymphomas.[10] Nor are there any known risk factors for progression of LyP. However, Querfeld et al discuss data using increased fascin levels, coexpression of CD30/56 and loss of CD134 as possible predictors of disease progression. Further investigation into mechanisms of disease progression is needed to design innovative treatment approaches for these diseases.

Future Directions

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Given the importance of molecular characterization in the categorization of T-cell lymphomas, a further description of the steps by which these tumors undergo apoptosis and malignantly transform is clearly needed. Querfeld et al include an impressive discussion regarding molecular and biologic properties currently under investigation for specific PCLPDs. Many of the cited concepts are the foundation for the future of PCLPD research.

One intriguing approach involves targeting the apoptotic functions of CD30 and the proapoptotic protein Bax with our understanding of the waxing and waning nature of LyP lesions. Preliminary results from CD30 antibody targeting in PCLPD has shown some success.[11] Another group identified endogenous retroviral elements in PCLPD biopsies and postulated that these may represent an unknown infectious agent associated with the pathogenesis of PCLPD.[12] Microdissection techniques are being used to explore the proliferation and transformation of these tumor types and is an attempt to work around the known biologic heterogeneity seen in these lesions.[13] This research may enhance our understanding of the skin-homing of PCLPD malignant T cells through specific cell-surface markers, as well as the cytokine milieu, further identifying novel targets for therapy.

Conclusions

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The article by Querfeld et al nicely summarizes the newest insights in the biology, diagnosis, and treatment of PCLPD. Additional research needs to be done regarding specific diagnostic testing, and understanding transformation triggers from LyP to more aggressive lymphomas. Due to the rarity of these diseases, further clinical collaboration between the dermatology and oncology communities regarding research approaches to treatment and prevention is essential. It is clear that we are in a new era for the classification and treatment of these complex disorders, and the review by Querfeld and colleagues documents the beginning of this journey.

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