Comment on Cohen et al, page 2753

Deciphering hydroa vacciniforme

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In this issue of *Blood*, Cohen et al describe a series of hydroa vacciniforme (HV)–like lymphoproliferative disorder (HV-LPD) cases in whites; they confirm that HV-LPD is an Epstein-Barr virus (EBV)–related lymphoproliferation with earlier disease onset and lower EBV DNA levels in blood with a lower risk of developing a systemic disease when compared with nonwhites.[1]

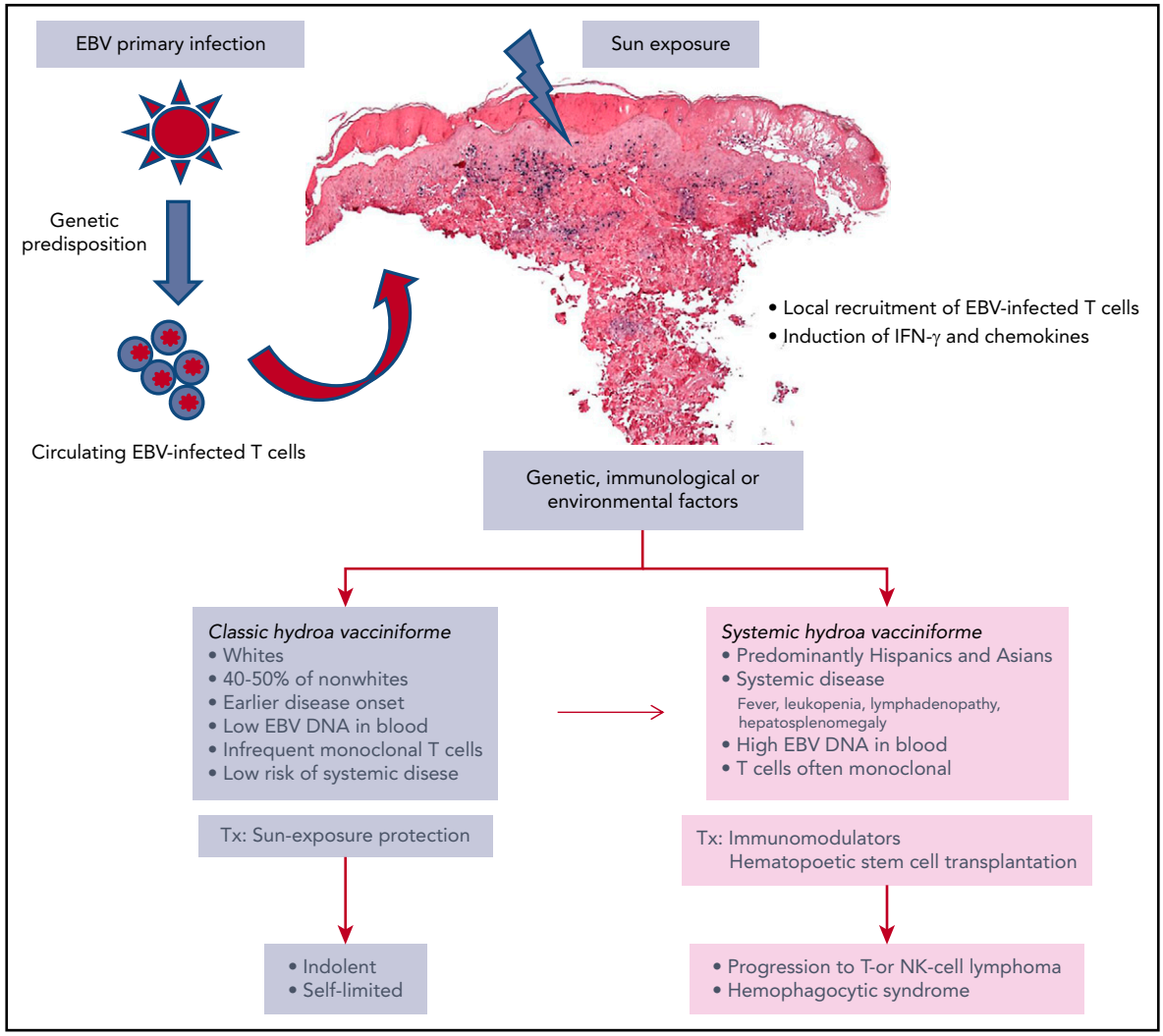
HV was originally described in western countries as a benign photodermatosis characterized by light-induced vesicles that evolve to crusts and leave varicelliform scars after healing.[2] Systemic symptoms are not observed and the disease often resolves spontaneously in adolescence or young adulthood. A similar, but clinically more severe, disorder has been described mainly in children from Latin America and Asia.[3-5] These patients often present with marked facial edema, multiple vesicles, large necrotizing ulcers, and severe scarring in sun-exposed and nonexposed skin areas accompanied by systemic symptoms including fever, lymphadenopathy, and hepatosplenomegaly. Later studies demonstrated that these lesions, which were termed "severe" HV to distinguish them from the more benign "classic" form described in western countries, were associated with EBV infection of T and/or natural killer (NK) cells and often showed monoclonal rearrangements of the T-cell receptor genes; therefore, the term "HV-like lymphoma" was suggested.[6,7] Based on these distinctive features, HV-like lymphoma was incorporated for the first time in the 2008 World Health Organization (WHO) classification of lymphomas as a subgroup of EBV$^+$ T-cell lymphoproliferative disorders of childhood. Nevertheless, due to the broad clinical spectrum of the disease and the lack of reliable morphological and molecular criteria to predict its clinical behavior, the term HV-like lymphoproliferative disorder was proposed to avoid the designation as lymphoma, and was incorporated into the revised fourth edition of the WHO lymphoma classification.[8]

Because "classic" HV in western countries is very rare and considered a benign, self-limited photodermatosis, the skin lesions are rarely biopsied; and therefore, T-cell clonality or EBV status has not been thoroughly investigated. Nevertheless, it has been assumed that "classic" HV in western countries might belong to the same disease spectrum as cases from Latin America and Asia; however, data are sparse to corroborate this assumption. In the current study, Cohen et al confirm that HV in white patients from the United States and England is, in fact, an EBV-associated lymphoproliferative disorder affecting T and/or NK cells, but occurring in younger patients with a more benign clinical presentation and evolution when compared with nonwhites. Most white patients in this series had an indolent clinical course with or without treatment and irrespective of the demonstration of T-cell clonality, although whites were less likely to develop T-cell clones. This finding highlights the fact that the demonstration of a T-cell clone is not predictive of an aggressive course in patients suffering from HV-LPD, and should not be used as evidence for a malignant lymphoid proliferation.[4] In contrast, nonwhites present often with more severe cutaneous lesions, systemic symptoms, leukopenia, and high levels of EBV DNA in blood and may progress to a full-blown T- or NK-cell lymphoma/leukemia or develop hemophagocytic syndrome. Although patients with HV-LPD and systemic symptoms might have a temporary response to immunomodulators like thalidomide, corticosteroids, or hydroxychloroquine, only hematopoietic stem cell transplantation has been shown to be curative.[9]

The differences in clinical severity and the significantly higher incidence of HV-LPD in patients of distinct ethnic origin are in line with other observations concerning EBV-associated T- and NK-cell lymphoproliferations, such as extranodal NK/T-cell lymphoma, nasal type, the prototypic EBV-associated disorder in Asians and Hispanics. This and the more indolent disease in whites indicate that genetic background and/or environmental differences might be responsible for the spectrum of clinical presentations observed in this disorder. The model suggests that patients with a particular genetic background after primary EBV infection can develop a chronic state characterized by the persistent presence of EBV-infected cytotoxic T cells and/or NK cells that, in response to inflammatory stimuli, such as sun exposure or mosquito bites, are recruited locally and lead to subsequent tissue damage. Additional genetic, immunological, or environmental events might be responsible for the more aggressive clinical behavior in a fraction of these patients (see figure).

Another interesting aspect of the study was the upregulation of interferon-γ (IFN-γ) and multiple genes that encode chemokines including CXCL11 (I-TAC), CXCL10 (IP10), CXCL9 (MIG), and CCL4 (MIP1β), which attract activated monocytes, T cells, and NK cells, demonstrated by RNA sequencing in the skin lesion of 1 white patient. However, this was shown to be a local phenomenon, as the mean serum levels of cytokines tested in HV-LPD patients were similar to healthy controls, in contrast to patients with chronic active EBV infection, systemic form. Nevertheless, the observed local chemokine upregulation in the lesional skin of HV-LPD suggests that these chemokines, and potentially polymorphisms in genes encoding for chemokines and their receptors, might contribute to the severity of this EBV-associated disease, warranting further investigation.[10] Future studies should address this question by comparing the chemokine profile from skin lesions of "classic" HV patients vs the more severe forms and whites vs nonwhites.

In conclusion, this study demonstrates that HV-LPD in whites is an EBV-associated disorder with rather indolent clinical behavior and good response to reduction of sun exposure only. The question of whether "classic" HV without EBV association exists at all remains. It is probably time to rename this disease as HV



Putative pathogenesis of HV-LPD. Individuals with a particular genetic background after primary EBV infection develop a chronic state characterized by the presence of EBV-infected T cells. Circulating EBV-infected T or NK cells are recruited to the skin and activated following sun exposure. Local production of IFN-γ and chemokines results in inflammation and tissue damage. The skin biopsy shows epidermal reticular degeneration leading to intraepidermal spongiotic vesiculation. The lymphoid infiltrate predominates in the dermis around adnexae and blood vessels. The lymphoid cells are positive for EBV (in black), as demonstrated by in situ hybridization for EBV-encoded small RNA. Due most probably to additional genetic, immunological, and/or environmental factors, a subset of patients mostly of Asian and Hispanic ethnicity may develop severe disease with systemic involvement, whereas the remainder show an indolent, self-limiting course. Rare patients with an indolent presentation may progress after years to the more severe form of HV-LPD with systemic symptoms. HV-LPD with systemic symptoms has been referred in the literature as "severe" HV or HV-like lymphoma. Tx, treatment.

EBV-associated LPD, encompassing the broad clinical spectrum that can be encountered in this enigmatic disease.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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LYMPHOID NEOPLASIA

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A one-two punch with VO KOs CLL

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In this issue of *Blood*, Flinn et al report the results of a phase 1b study combining venetoclax and obinutuzumab (VO) to treat both relapsed/refractory and previously untreated chronic lymphocytic leukemia (CLL).[1]

Targeted therapy has come of age in the treatment of CLL, first with the addition of anti-CD20 monoclonal antibodies including rituximab and obinutuzumab to chemotherapy, followed by small molecule inhibitors blocking critical signaling pathways or overexpressed antiapoptotic proteins. Ibrutinib has been shown to irreversibly inhibit Bruton tyrosine kinase in the B-cell receptor signaling pathway. Continuous treatment with ibrutinib monotherapy has shown dramatic efficacy in both untreated and previously treated CLL patients.[2] Venetoclax, a potent inhibitor of B-cell lymphoma 2 (BCL-2), restores normal apoptosis in CLL cells and was initially approved for previously treated CLL patients.

The need for continuous therapy with ibrutinib monotherapy is highlighted by the low rate of complete responses (CRs), largely due to persistent disease in the bone marrow (BM). Very little is known about the durability of response after stopping ibrutinib in patients who stop for reasons other than disease progression. The addition of rituximab to ibrutinib did not prolong response despite higher CR rates and more frequent undetectable minimal residual disease (uMRD).[3]

In the phase 3 iLLUMINATE trial for previously untreated patients, the combination of ibrutinib and obinutuzumab demonstrated superior progression-free survival compared with chlorambucil and obinutuzumab (ChlO). But only ~20% of subjects achieved uMRD responses in the BM, and there was no significant difference between the 2 groups.[4] Given these results, it is doubtful that the addition of obinutuzumab could facilitate time-limited therapy when combined with ibrutinib.

Venetoclax has also been used as continuous monotherapy in trials of high-risk patients with relapsed or refractory CLL, and there are reports of even high-risk patients maintaining their response after stopping treatment. The largest reported experience is the MURANO trial, which randomized previously treated patients to bendamustine and rituximab vs venetoclax and rituximab.[5] Rituximab was given during the first 6 months of therapy while venetoclax was administered for a maximum of 2 years. With a median follow-up of 36 months, 71.4% of venetoclax/rituximab-treated patients were still free of progression with only 14% of patients receiving subsequent therapy. This combination also achieved deep responses, with uMRD in 64% of patients who completed 2 years of treatment without progression. This depth of response was clinically meaningful, with 97.6% of patients with uMRD remaining free of progression with median follow-up of 10 months after stopping therapy, compared with only 62% with detectable MRD.

At present, the role of combination therapy remains unclear, especially in previously untreated patients. A phase 1b study involving only 12 patients showed that ibrutinib, obinutuzumab, and venetoclax could be given in patients with relapsed CLL, with 6 patients achieving uMRD responses after 12 months of therapy.[6] The same group reported their preliminary results of this same combination in an expanded cohort of relapsed patients as well as in a treatment-naive cohort.[7] Two-thirds of the 25 treatment-naive patients and one-half of the 25 relapsed patients achieved uMRD at the end of therapy.

The combination of venetoclax and ibrutinib has been studied in 2 phase 2 trials involving treatment-naive patients with equally impressive results.[8,9] In the first trial, treatment duration in 80 patients was 12 months with no patient progressing from CLL. After completion of treatment, 61% had no detectable CLL in their BM. In the second trial, 163 patients were treated, with 9 of the first 11 achieving BM uMRD. A third study using this combination in 49 relapsed patients demonstrated a 39% BM uMRD response after 12 months of treatment.[10]

The study by Flinn et al in this issue describes the use of obinutuzumab with venetoclax to treat CLL. In the treatment-naive group of 32 patients, 78% achieved a CR or CR with incomplete count recovery and 78% achieved uMRD in the BM after 6 months of obinutuzumab and 12 months of venetoclax. In the relapsed group of 46 patients, 62% achieved uMRD in the BM, although these patients were eligible to continue venetoclax monotherapy indefinitely. These are the highest rates of uMRD reported with combination therapy.

A subsequent phase 3 randomized trial of VO vs ChlO in treatment-naive CLL patients demonstrated superior progression-free survival in favor of VO with 57% of 216 patients achieving uMRD in the bone marrow with sustained uMRD responses 12 months after treatment completion.[11] As a result, venteoclax is now approved in the US for all patients with CLL.

Like a prize fighter in the early rounds of a championship bout, an early knockdown can be game-changing. Combinations of novel, targeted drugs with differing mechanisms of action are entering the ring as formidable challengers to monotherapies. Will a winner emerge? And can we rely on time-limited therapy? Venetoclax with obinutuzumab provides a knockout (KO) punch to CLL. Can it arise again to fight another day?