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Epstein- Barr Virus and Lymphoproliferative Diseases of the Skin

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Epstein-Barr virus (EBV) is an ubiquitous virus and several malignancies including Burkitt’s lymphoma, nasopharyngeal carcinoma and post-transplant lymphoproliferative disorders are related to EBV infection. Primary EBV infection is usually asymptomatic but it sometimes progresses to infectious mononucleosis (IM), which resolves spontaneously after the emergence of EBV-specific immunity. Typically, immunocompetent hosts develop EBV-specific immunity especially EBV-specific cytotoxic T lymphocytes (CTL) to control the outgrowth of EBV transformed cells during the primary infection and the long-term carrier state but in some apparently immunocompetent hosts, chronic infections can develop.

Most primary EBV infections resolve spontaneously, but in some cases EBV can cause chronic infections in immunocompetent hosts. Chronic active EBV (CAEBV) infection is defined as a persistent EBV infection with an unusual pattern of EBV-related antibodies and high viral loads in the peripheral blood. The antibody profile is characterized by elevated immunoglobulin G (IgG) viral capsid antigen (VCA) titers with positive anti-EBNA and negative IgM-VCA antibodies.

CAEBV infection is characterized by chronic or recurrent IM-like symptoms, and is associated with life-threatening complications, including virus associated hemophagocytic syndrome, interstitial pneumonia, lymphoma, coronary artery aneurysms, and central nervous system involvement. The clonal expansion of EBV-infected T cells and NK cells appears to play a central role in the pathogenesis of CAEBV infection. Hypersensitivity to mosquito bites and severe hydroa vacciniforme (HV) like eruptions have also been associated with CAEBV. Symptoms include non-exudative pharyngitis, cervical and submandibular lymphadenopathy and splenomegaly.

None sexually related acute genital ulcers (NRAGU), so called Lipschutz, ulcers are painful ulcerations of the external genitalia occurring primarily in adolescent females, with a mean age of onset of 14.5 years. They are often misdiagnosed as herpes simplex virus infection or Behcet disease and may prompt an evaluation for sexual abuse, causing significant physical and emotional distress for the patient and parents. Incidence between 10% and 30% among adolescent women has been reported, but this is likely an underestimate. Patients typically present very painful ulcers with characteristic purple-red ragged edges, most commonly on the medial or outer surface of the labia minora. Less commonly, involvement of the labia majora and extension onto the proximal thighs has been reported. Lymphadenopathy distant from the site of ulceration is common. Nonspecific prodromal symptoms often precede the appearance of ulcers and most patients will eventually develop the characteristic symptoms of IM. In one case series, 70% of cases had a history of oral aphthosis. NRAGUs related to EBV usually occur as a solitary episode, a feature that distinguishes them from herpes and aphthosis, which tend to be recurrent. NRAGU is a self-limiting condition, usually resolving spontaneously within 2 to 6 weeks without scarring. Treatment is supportive and may include pain control, topical corticosteroids, and short courses of oral prednisone. Histologically, there is vasculitis with a mixed cell infiltrate and overlying ulceration. Diagnosis relies on excluding other causes of genital ulceration and detecting EBV DNA by PCR on vulvar swabs or confirming acute EBV infection serologically.

Hypersensitivity to mosquito bites (HMBs) is a disease associated with chronic EBV infection and is characterized by intense local cutaneous reactions including erythema, bullae, necrosis, and ulceration. Systemic symptoms, including high-grade fever, malaise, lymphadenopathy, hepatic-splenomegaly, hepatic dysfunction, hematuria, and proteinuria, often accompany the cutaneous reaction. Most cases have been reported from Japan, Taiwan, Korea, and Mexico. The majority of cases occur within the first 2 decades of life, with a median age at diagnosis of 6.7 years. HMB can be distinguished from a simple allergic reaction to mosquito bites by the severity of the cutaneous reaction and associated systemic symptoms. HMB has been reported to have a strong association with chronic EBV infection and NK/ T-cell leukemia/lymphoma. It has also been observed in none EBV-related lymphoproliferative diseases, The reaction resolves spontaneously, usually healing with a scar. Treatment is symptomatic, and repeated episodes occur with future mosquito bites. Regular clinical follow-up of patients with HMB is recommended to assess for the development of lymphoproliferative disease.
Hydroa vacciniforme (HV) is a rare childhood photosensitivity disorder of unknown pathogenesis. Mild burning, stinging, or pruritus is common within 6 hours of sun exposure, and mild conjunctivitis or keratitis is not uncommon. Rare features include photoonycholysis, earlobe mutilation, and partial absorption of bone. The differential diagnosis includes erythropoietic protoporphyria, polymorphous light eruption, actinic prurigo, and porphyria cutanea tarda. HV can be distinguished from erythropoietic protoporphyria and porphyria cutanea tarda by testing for porphyrin levels. The histopathology of HV reveals intraepidermal vesiculation with reticular degeneration, progressing to confluent epidermal necrosis in later lesions. A dense perivascular lymphohistiocytic infiltrate may be present in the dermis. Direct immunofluorescence is usually negative, but may rarely show scattered granular deposits of C3 at the dermoepidermal junction.

Hydroa vacciniforme-like lymphoma (HVLL) is a rare EBV cutaneous T-cell lymphoma occurring predominantly in children and adolescents from Asia, Central America, South America and Mexico. In addition to the characteristic vesiculopapules of classical HV, HVLL presents with marked facial edema, large ulcerative cutaneous lesions, hemorrhagic bullae, atrophic scars, and severe disfigurement in both sun-exposed and photoprotected areas. Unlike HV, lesions are not induced by sun exposure and typically do not resolve spontaneously with age. HVLL was initially considered to be a severe atypical variant of HV, but subsequent research revealed that the majority of lesions contain monoclonal T-cell receptor gene rearrangements. Microscopic evaluation of cutaneous lesions reveals a perivascular and periadnexal lymphocytic infiltrate of atypical small to medium cells in the papillary and reticular dermis, occasionally extending into the subcutis. Vasculitis, angiodestruction, and necrosis may also be present. Neoplastic cells often have a CD8 cytotoxic T-cell phenotype expressing TIA-1, granzyme B, or perforin. Less commonly, cells are CD56, indicating an NK/T-cell phenotype. In cases with an NK/T-cell phenotype, the lymphocytic infiltrate often involves the subcutis, mimicking subcutaneous panniculitis-like T-cell lymphoma. Rare cases of CD4 cytotoxic T-cell phenotype have been reported. EBER ISH is consistently positive, while LMP1 is only expressed occasionally. HVLL follows a variable disease course; recurrent skin lesions, intermittent fever, and hepatosplenomegaly may persist. More aggressive clinical course is associated with progression to the hemophagocytic syndrome and NK/T-cell lymphoma. This entity is relatively rare, and standardized treatment protocols have not been developed. Therapies that have been used previously in the treatment of HVLL include interferon-alfa, systemic steroids, cyclosporine, intravenous immunoglobulin, combination chemo-therapy, and radiation.
From inflammation to neoplasia - Distinguishing between lupus erythematosus panniculitis and subcutaneous panniculitis-like T-cell lymphoma

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Since subcutaneous panniculitis-like T-cell lymphoma (SPTCL) involves the lobules of the subcutis, since sometimes the lymphocytes in SPTCL are not particularly atypical and since lupus erythematosus panniculitis (LEP) is a lobular panniculitis mostly of T-cells, it can at times be difficult to distinguish SPTCL from LEP. The following features have been reported in the literature to favor LEP over SPTCL: concurrent clinical and/or histopathologic features of LE, the presence of reactive germinal centers, septal fibrosis, numerous plasma cells, negative TCR and the presence of clusters of plasmacytoid dendritic cells.

In our experience, the most useful discriminating feature between these conditions is the proliferation rate of lymphocytes rimming adipocytes as assessed by Ki-67. In a study we performed, in 15/19 cases of SPTCL, the Ki-67 rate was > 25% in the lymphocytes rimming adipocytes but never greater than 25% in the cases of LEP. We also showed that dermal mucin deposition, plasma cell aggregations and clusters of CD123 plasmacytoid dendritic cells could be seen in SPTCL while, in a sizable number of cases, the lymphocytes rimming adipocytes in LEP were CD8+. Therefore, in our experience, the following are not reliable discriminating features between these two conditions: dermal mucin deposition, plasma cell aggregations, clusters of CD123 plasmacytoid dendritic cells or CD4 versus CD8 labeling.

Although the above discusses discriminating features between SPTCL and LEP, there are rare cases that show features of both diseases and therefore some patients probably have both diseases concurrently. Therefore, LEP can probably evolve into SPTCL in some instances.

References:

The old & the new provisional entities in the 2015 WHO classification

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Two specific entries in the current WHO lymphoma classification remain in the provisional category, despite accruing evidence for their claim as bona fide diseases; aggressive epidermotropic CD8(+) (“Berti’s”) lymphoma and small medium pleomorphic CD4(+) lymphoma (SMPTCL). A further well documented indolent CD8(+) lymphoid proliferation of acral sites has yet to find recognition in the classification, despite over 40 cases now described in the literature. Berti’s lymphoma presents in most cases with a short history of plaques and tumours, and in rare instances as one or few tumours, has a pagetoid reticulosis histology and in addition to CD8 expression, typically a CD2(-) CD5(-) high Ki-67 immunophenotype; most are CD45RA(+). The prognosis is dismal. After Berti’s 1999 seminal paper documenting the disease there have been numerous case reports, with the largest case series of 18 patients recently published by an EORTC working group1; this paper and Nofal et al2, are the first to propose diagnostic criteria, and provide further evidence that it is distinct from CD8(+) examples of mycosis fungoides. SMPTCL is more controversial, raising two recurring questions. 1. Is it an entity? 2. If so, is it a lymphoma? Evidence for a distinct process is reasonably compelling; a characteristic presentation as a single tumour, often clinically suspected as B-cell lymphoma, a dense infiltrate with cytological atypia, a significant follicular T-helper cell population on immunohistochemistry, and a T-cell clone. The nature of the process is more difficult and contested; similarly dense infiltrates can be seen in various settings e.g. insect bites, and SMPTCL probably has a 100% survival. At least one paper suggests that inflammatory conditions of known aetiology do not contain appreciable numbers of FTH cells and therefore if SMPTCL is a reactive condition it is a distinct & reproducible process. Indolent CD8(+) lymphoid proliferation of acral sites was first described by Petrella et al 20053; now there are 40 documented cases, most of which arise on the ear, have a cytotoxic clonal phenotype but wholly indolent clinical course. Whilst some authorities prefer to consider this a CD8 variant of SMPTCL there are a number of differences, the most important of which is the lack of TFH cells in the limited number of cases evaluated. The existence of recurrent clonal cytotoxic proliferations within the gut set a precedent for this entity as early as 1998.

All three of the entities listed have reproducible clinicopathological characteristics and are likely to attain definitive nosological status in future revisions of the WHO classification.

CD30 – everywhere?

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CD30 is a cytokine receptor, which belongs to the tumor necrosis factor superfamily receptors. It turned out not only to be a diagnostic marker for certain non-Hodgkin lymphomas, but also to be directly engaged in the growth of CD30-positive lymphoid tumor cells.

Expression of CD30 by atypical lymphocytes defines the group of cutaneous CD30-positive lymphoproliferative disorders (CD30+ LPDs) including lymphomatoid papulosis (LYP) and primary cutaneous anaplastic large cell lymphoma (PCALCL). in PCALCL expression of CD30 by more than 75% of the tumor cells is required. Despite the cytomorphology in most manifestations of cutaneous CD30+ LPDs suggest high-grade malignancy, the course of these disorders is characterized by a favorable prognosis.

CD30 expression is not only limited to the group of cutaneous CD30+ LPDs, but can also be observed in various other forms of cutaneous and extracutaneous T- and NK/T-cell lymphomas as well as rare forms of B-cell lymphomas, particularly EBV-associated B-cell lymphoproliferations in immunosuppressed patients. In mycosis fungoides (MF), the prognostic impact of CD30 varies depending on the evolutionary stage of the disease. In early MF expression of CD30 by a significant number of dermal lymphocytes in conjunction with a high proliferation rate of dermal lymphocytes indicates an impaired prognosis, whereas expression of CD30 in advanced disease stage, i.e. tumor stage, goes along with a longer overall survival.

In rare T-cell lymphomas such as cutaneous gamma/delta T-cell lymphoma or extranodal NK/T-cell lymphoma, nasal type, expression of CD30 is occasionally found and may result in diagnostic difficulties to distinguish those lymphomas from cutaneous CD30-positive LPDs, especially if the latter ones manifest with unusual histological features such as angiocentric and angiodestructive growth (e.g. LyP type E). No clear-cut association of CD30 expression in these rare forms of T and NK/T-cell lymphomas with prognosis so far could be established.

Apart from the expression of CD30 in lymphomas, the presence of CD30-positive enlarged lymphoid cells has also been documented in reactive processes such as arthropod bite reactions, drug eruptions and infectious processes, in which the expression of CD30 indicates activation of the involved lymphocytes. These disorders represent differential diagnoses to LYP type A.

Due to the broad differential diagnoses and the wide spectrum of diseases which can harbor CD30-positive cells, additional markers are needed to allow distinction between the different lymphoma entities and benign and malignant processes. Such markers include for example 5hmC, which turns out to be helpful in the distinction between reactive and neoplastic processes with CD30 expression.

CD30 is not only expressed by the tumor cells in various forms of lymphomas, but also in certain non-lymphoid neoplasms such as vascular tumors, particularly angiosarcoma. Its relationship to the biology of these disorders remains to be elucidated.

Finally apart from being a diagnostic and prognostic marker, CD30 acts as a target for anti-CD30-antibody based treatment modalities such as brentuximab vedotin. Remarkably the number of CD30-positive cells only weakly correlates with the response to those pharmacological approaches. I MF expression of CD30 by more than 5% of the tumor cells may be sufficient for a response to brentuximab vedotin. These findings imply that evaluation of the expression of CD30 in various lymphomas and potentially other neoplasms has diagnostic, prognostic and therapeutic implication. It also underlines the necessity for standardization of the immunohistochemical assessment of CD30 expression in the near future.

References:


"The information contained in the "Cutaneous Lymphoproliferations - an update 2016" handout is not intended as medical advice or consultation, and should not be relied upon as such".