Case Presentation 19

A PD-1 CD4 Positive Lymphomatoid Vascular Reaction Most Suggestive of Sézary syndrome

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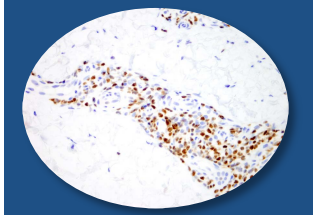
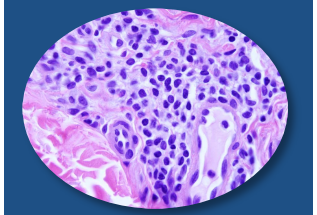
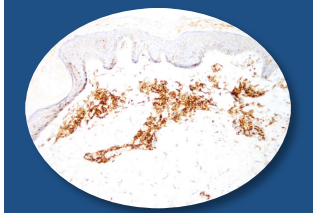
Weill Cornell Medicine Dermatopathology







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Case Report

A 36 year old female presented to her primary care physician with pruritic rash on the inner thighs of 7 months duration. She had a history of multiple miscarriages, and therefore had peripheral blood cytogenetics and extensive autoimmune workup from 2014 which were negative. Despite applying triamcinolone topical cream and taking hydroxyzine for 1 month, her pruritis worsened and extended to the hands and feet. Physical examination revealed scattered hyperpigmented patches over the thighs, arms, abdomen, and back. Hyperkeratosis was observed on the palms and soles.

Histopathological Features

Punch biopsies taken from the bilateral arms revealed a predominantly angiocentric atypical lymphocytic infiltrate in the superficial and mid dermis with minimal epitheliotropism (Figures A and B). There was some degree of permeation of the interstitium superficially with attendant subepidermal fibrosis. The infiltrate was predominated by small to intermediate sized lymphocytes showing nuclear contour irregularity including many cells with hyperconvoluted cerebriform nuclei (Figure C). Few plasma cells were identified as well. There was a concomitant mild epidermal hyperplasia surmounted by an orthohyperkeratotic scale. While the infiltrate was not significantly epidermotropic there is very focal folliculotropism, whereby interfollicular collections of cerebriform lymphocyte really defining an interfollicular Pautrier's microabscess were identified.

Immunohistochemical Findings

Comprehensive phenotypic studies were performed. The lymphocytic infiltrate was extensively highlighted by CD3 and pan T-cell marker CD2. The CD4 to CD8 ratio showed a clear-cut predominance of CD4 T-cells over those of the CD8 subset with a CD4 to CD8 ratio that is in excess of 5 to 1 (Figures D and E). The lymphocytes were of the alpha beta subset based on the extent of immunoreactivity for BetaF1. There was striking and extensive immunoreactivity of the lymphocytes for PD1 (Figure F). There was marked upregulation of TOX amidst the lymphocytes (Figure G) including strong nuclear expression of TOX amidst angiocentric lymphocytes. There was focal staining for CD25 (20 to 30% of the infiltrate) and the CD7 preparation showed a significant decrement in staining (20 to 30% of the infiltrate) (Figure H). There were a few FOXP3 positive staining T-cells but the majority of the cells did not exhibit a regulatory T-cell phenotype. .

Discussion

Sézary syndrome is characterized by the triad of erythroderma, lymphadenopathy, and abnormal T cells (Sézary cells), in the peripheral blood, lymph nodes, and skin. The authors of the 2005 WHO-EORTC classification for cutaneous lymphoma suggested that there must be an absolute criterion, which is one of established T cell clonality in the peripheral blood and skin, ideally demonstrating the same T cell clone (Willemze et al. 2005). The authors proposed two additional criteria, of which at least one must be present; the first is both cytomorphologic and quantitative, requiring a count of 1000 or more Sézary cells per square millimeter in the peripheral blood. The second criterion is immunophenotypic; the CD4 to CD8 T lymphocyte ratio in the peripheral blood must be in excess of 10:1, with a concomitant loss of pan T cell markers such as CD2, CD3, CD7, and CD5 (Willemze et al. 2005, Vonderheid et al. 2006).

The histopathology is not characteristic for mycosis fungoides as it is a predominantly angiocentric atypical lymphocytic infiltrate with minimal epitheliotropism whereby there is focal infiltration of the hair follicle by atypical cerebriform lymphocytes. In contrast, this minimally epitheliotropic lymphocytic infiltrate with a dominant lymphomatoid vascular reaction, whereby the atypical lymphocytes show CD4 positivity with a loss of CD7 and overexpression of PD1 is very characteristic for Sézary syndrome. Unlike mycosis fungoides where one expects to see conspicuous epidermotropism, including Pautrier's microabscesses, biopsies in the setting of Sézary syndrome may be minimally epidermotropic. Instead, the infiltrate of Sézary syndrome lies largely within the dermis, exhibiting a vasocentric disposition around vessels of the superficial vascular plexus.

The expression in this case of Programmed death-1 (PD-1) is critical. PD-1 is an inhibitory member of the CD28/CTLA-4 family. The PD-1 pathway exerts its function through inhibiting TCR-mediated T cell proliferation and cytokine production. PD-1 has been useful in differentiating Sézary syndrome from erythrodermic inflammatory dermatoses when expressed in CD4+ T cells over CD8+ T cells (Çetinözman et al. 2014). Biopsies of Sézary syndrome typically show very prominent expression of PD-1 that far exceeds that in mycosis fungoides (Çetinözman et al. 2012). It has postulated that Sézary syndrome is really a neoplasm of central memory T-cells and differs from conventional mycosis fungoides in which the cell of origin is held to be a resident effector T cell. Due to the abnormal pattern of PD-1 staining, a reactive based etiology including in the context of a lymphomatoid drug reaction is not favored.

In summary, the biopsies show a PD-1 and CD4 positive lymphomatoid vascular reaction most suggestive of Sézary syndrome. The diagnosis of Sézary syndrome in this case does rest on correlation with the peripheral blood findings and the overall quality of the skin eruption. With erythrodermic mycosis fungoides the patients do not fulfill peripheral blood criteria to warrant categorization of Sézary syndrome. These patients oftentimes do have long standing mycosis fungoides. The patient should have peripheral blood studies done to determine whether or not this patient actually fulfils peripheral blood criteria to warrant the categorization of this atypical process as one of Sézary syndrome. If the patient does not have an established history of mycosis fungoides this process may have arisen in a de novo fashion or possibly in a background of idiopathic erythroderma where there frequently is a hyperkeratosis of the palms and soles.

Figure Legend

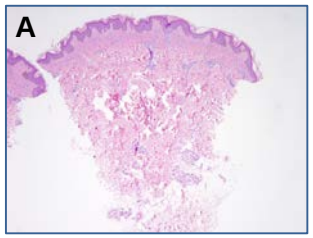

Figure A. This low-power view shows a superficial dermal lymphocytic infiltrate..

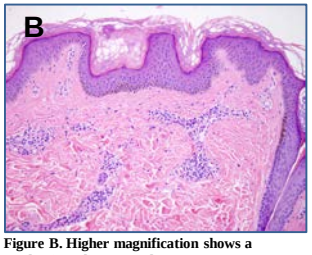

Figure B. Higher magnification shows a predominantly non-epidermotropic lymphomatoid vascular reaction, without angiodestructive changes, accompanied by a benign pattern of epidermal hyperplasia. There are rare lymphocytes noted within the epidermis and hair follicle.

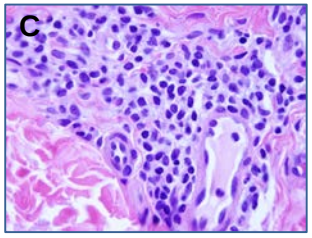

Figure C. Examination under oil shows the markedly hyperconvoluted nature of the lymphocytes.

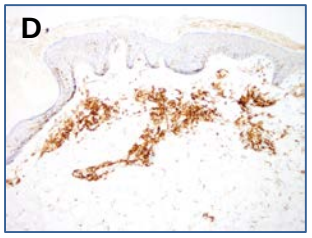

Figure D. The infiltrate is predominated by CD4 positive cells.

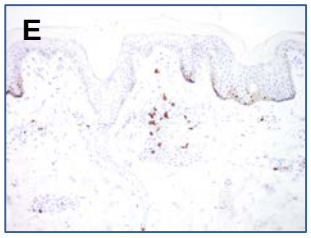

Figure E. The CD8 preparation shows only a few positive staining cells in the infiltrate. Overall, the CD4 to CD8 ratio is abnormal, exceeding 5:1. The few CD8 lymphocytes present are typically reactive in nature and represent part of the counter-regulatory lymphocytes that play some role in the attenuation of autonomous clonal T cell expansion.

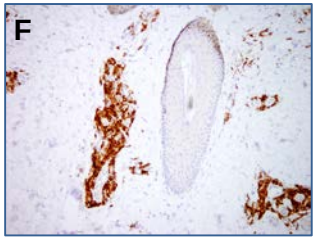

Figure F. There is extensive staining of the angiocentric infiltrate for PD1

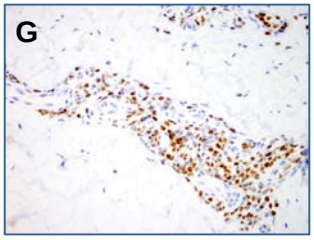

Figure G. There is strong nuclear staining of TOX amid the angiocentric lymphocytes.

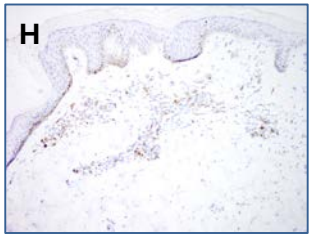

Figure H. There is a marked reduction of CD7. Only 20-30% of the infiltrate is positive.

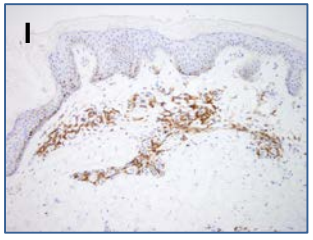

Figure I. There is nuclear staining for NFAT, while all of the T cells show cytoplasmic immunoreactivity for NFAT.

Case References

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Under the direction of Dr. Cynthia M. Magro, the Weill Cornell Comprehensive Dermatopathology Service is a leading edge consultation service and CAP-accredited laboratory for dermatologists, plastic and general surgeons and other dermatopathologists. Dr. Magro is an internationally renowned dermatopathologist, educator and author. She is a Professor of Pathology and Laboratory Medicine at the Weill Cornell Medical College in Manhattan, and is board certified in anatomic pathology, dermatopathology and cytopathology. Dr. Magro is an expert in the diagnosis of complex inflammatory skin diseases. Her areas of expertise include cutaneous manifestations of auto-immune disease, systemic viral disease and vasculitis, atypical drug reactions, benign, atypical and overtly malignant lymphocytic infiltrates of the skin, and diagnostically difficult melanocytic proliferations.The award-winning author of *The Melanocytic Proliferation: A Comprehensive Textbook of Pigmented Lesions*, Dr. Magro has recently completed her second book, *The Cutaneous Lymphoid Proliferation, a comprehensive textbook on benign and malignant lymphocytic infiltrates*. She has co-authored over 280 peer reviewed papers and several textbook chapters. Dr. Magro frequently presents courses on inflammatory skin pathology and difficult melanocytic proliferations to the American Academy of Dermatology, the United States and Canadian Academy of Pathology, and the American Society of Clinical Pathology. Dr Magro has consistently been recognized in Who's Who in America®, Castle Connolly's renowned America's Top Doctors – New York Metro Area® edition and in the Super Doctors® list published in The New York Times Magazine.

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