Case Report

Immuno Pathogenesis of Pregnancy induced Lymphomatoid Papulosis

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Abstract
We present the immuno pathogenesis of Lymphomatoid Papulosis associated with mild immuno suppression. The foundation of our observation was based on case reports discussing the development of LyP while concurrently using immune modulators. The medically altered immune state is mirrored by the hormone-induced changes of pregnancy. Furthermore, we explain how the natural progression of pregnancy facilitates a pathologic transformation of LyP in rare individuals. This is only the second reported case of pregnancy induced LyP. To clarify the findings, we include a basic review of Lymphomatoid Papulosis with key points of immunology related to both pathology and pregnancy.

CASE DESCRIPTION
A 35-year-old Caucasian female G4P4 at week one post partum with no significant past medical history was referred to our clinic for evaluation and treatment of right thigh dermatitis. Reported history suggested a recurrent dermatitis in the same location of which she believed the papules had been larger during the previous flare. Physical exam confirmed the lesions were localized to the distal right thigh with a grouping of four 2-3mm erythematous macules, the larger papule with scales (Figure 1). Initial presentation and history placed prurigo nodularis as a top differential. A biopsy was agreed upon and later demonstrated the presence of CD4 cells, greater than 50% CD30 positive (Figure 2). A diagnosis of Lymphomatoid Papulosis (LyP) was suggested from the pathology, which correlated to her clinical picture. For further confirmation, gene rearrangement studies were requested from the biopsy.

The patient returned to clinic for Grand Rounds and further evaluation two weeks later. The patient denied systemic symptoms including fatigue, fever, chills or additional skin lesions. Additional medical history revealed an enlarged thyroid under investigation by her obstetrician. The skin lesion was predominantly unchanged with the previous biopsy site healing well. A second biopsy was obtained, which failed to demonstrate the presence of CD4 cells, greater than 50% CD30 positive (Figure 2). A diagnosis of Lymphomatoid Papulosis (LyP) was suggested from the pathology, which correlated to her clinical picture. For further confirmation, gene rearrangement studies were requested from the biopsy.

The patientlly subgroup C confirmed the diagnose COMPLETE. laboratory count, free T4, thyroid stimulating hormone. Ultrasound images of the thyroid noted a 5.1cm nodule in the left lobe. The patient was later evaluated by fine needle aspiration and found negative for thyroid malignancy (Figure 3).

DISCUSSION
LyP during pregnancy has only been documented once previously. In Yamamoto patient, it was suggested that the pregnancy had induced an LyP eruption [1]. Similarly, our patient noted a localized papulosquamous eruption during her recent pregnancy. Her prior dermatologic eruptions may or may not have been associated with other gestations; the timing and duration of prior eruptions were unclear. For this reason, our patient likely had an undiagnosed or chronic LyP that was

Figure 1 Right thigh image demonstrating erythematous macules and papules with scale and central ulceration.

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unmasked during pregnancy.

LyP is a rare disease with an incidence less than 2,000,000 people. Its hallmark is noted by a recurrent disease process with periods of relapse and remissions that can span from a few years to over a decade [2,3]. While LyP is self-limiting, 10-year survival rate of 100% [4], there is a strong correlation of LyP with the development of other lymphomas [4]. Approximately 40% of LyP may progress to another form of lymphoproliferative disorder with a predominance to mycosis fungoides (MF) [4]. Additional significant associations for LyP have been found with endocrinopathies and thyroid nodules [1,5].

Histologically, LyP can be further subclassified into 4 groups. Group A is noted to be of mixed infiltrate with a large population of predominately atypical CD30 positive cells. Group B has smaller atypical T lymphocytes and convoluted nuclei with a similar histologic presentation to MF. Group C, as noted in our patient, is often found to have large groupings of CD30 positive suggestive of an anaplastic lymphoma. Lastly, in more recent literature, the fourth subtype has been presented. Type D, where the presentation is histologically related to epidermotropic CD8 positive T-Cell lymphoma and CD30 negative [6].

Looking past the histopathological diagnosis, the immunopathogenesis of LyP may assist in unifying several key case reports in the literature. Three cases have been published describing therapies that invoked or exacerbated LyP through the use of an immune modulator: infliximab (TNF-α antagonist), rituximab (anti-CD20 in B-cells), and fingolimod (inhibit cytotoxic CD8 T-cells) [7-9]. These cases over LyP correlated with pathologic autoimmune response [7,9] and by immunosuppressive treatment for Chronic Lymphocytic Leukemia [8]. The immunological changes occurring in the above cases can be compared with the changes associated in pregnancy. We will cover the expected immune response in more detail to clarify pregnancy inducing LyP [1].

Often times the mechanism behind clinical presentation is misunderstood. Wong et al clarifies key aspects of immunopathogenesis with similar cutaneous lymphoproliferative disorders such as Cutaneous T-Cell Lymphomas (CTCL), specifically Mycosis Fungoides (MF) and Sezary Syndrome (SS) [10]. His research proposes that a progenitor T-cell (MF/SS) is capable of proliferation under the right conditions. These pathological processes induce shifts within the TH1/TH2 system; similar changes are appreciated through hormonal modulation of the immune system during pregnancy (Figure 4).

In MF/SS, the progenitor T-Cell within the skin demonstrates normal to increased expressions of inflammatory TH1 Cytokines during the early phases. The key cytokines of IL-2, IFN-γ, IL-12 allow for proliferation of the cell line. The increased levels of IL-2 up-regulate CD28 further allowing T-cell proliferation. As the malignancy advances, the malignant CD4 T-cell lines predominate causing a shift from the TH1 pro-inflammatory state to a TH2 anti-inflammatory state. Increasing levels of IL-4, IL-5, IL-10, and IL-13 govern this transition. The increasing levels of IL-10, and decrease in IFN-γ within the cytotoxic system further enable the shift towards TH2 predominance. The reduced anti-
tumor response allows the malignancy to evade the immune system [10].

Similarly, the early immune phase of pregnancy begins with an increase in the Th1 dominant system. The associated pro-inflammatory cytokines allow for implantation and early development. As the pregnancy continues, a shift towards the Th2 system is favored allowing for a period of permissive immuno tolerance of an allogenic fetus to the maternal system [11-13]. Pregnancy immune suppression is guided by increased levels of gonadotropins, particularly progesterone, estrogen, hCG, and AFP. The excess estrogen and progesterone favor the Th2 pathway by potentially suppressing T-cell activation and inducing effector T-cell apoptosis [11,12]. The role of T-regulatory cells in cancer pathology is divided due to its ability for both propagation and destruction of malignancies. Although the evidence is conflicting towards the exact mechanism, it is agreed that progesterone and estrogen are involved in the regulation of regulatory T-cells during pregnancy [12]. Given the general shift of the Th2 system and immuno tolerance during middle phases of pregnancy, T-regulatory cells are likely to be up-regulated during pregnancy allowing for propagation of LyP T-cells [13]. As mentioned previously, hCG and AFP are increased during this period. The role of hCG is reduction of IFN-γ and TNF-α [12] which are involved in tumor suppression via apoptosis and cytotoxic mediated tumor destruction. AFP further assists with the suppression of TNF-α. Simultaneously, hCG also increases levels of IL-10 [12], further suppressing the cytotoxic Th1 pathway. With our current understanding, it can be appreciated that faulty T-cells in conjunction with immuno suppression facilitates induction of LyP in rare individuals. By manipulating mediators of tumor suppression the immune system permits development of the fetus. It is during the same time where the pathological propagation, such as LyP, manifests. As the pregnancy hormones normalize after childbirth, so does the Th1/Th2 system. At this point, as indicated by our patient, the immune system is able to resume normal function and suppress activity of pathology such as LyP.

CONCLUSION

In addition to immune suppression, as in therapy for treatment of many dermatologic diseases, pregnancy is also a time of immunologic change. While the majority of pregnancies do not present with pathology, it is important to remember that this period of altered immune function may be an opportunity for disease to emerge. Consideration for biopsy should be addressed in select patients that present with recurrent or persistent dermatological processes. While LyP may be benign, a small percentage may go on to develop lymphoma, endocrineopathies or pathology that may require additional patient education and monitoring.

REFERENCES

1. Yamamoto O, Tajiri M, Asahi M. Lymphomatoid papulosis associated with pregnancy. Clin Exp Dermatol 1997; 22: 141-143.
2. Wang HH, Lach L, Kadin ME. Epidemiology of lymphomatoid papulosis. Cancer. 1992; 70: 2951-2957.
3. Wieser I, Oh CW, Talpur R, Ducic M. Lymphomatoid papulosis: Treatment response and associated lymphomas in a study of 180 patients. J Am Acad Dermatol. 2016, 74: 59-67.
4. de la Garza Bravo MM, Patel KP, Loghavi S, Curry JL, Torres Cabala CA, Cason RC, et al. Shared clonality in distinctive lesions of lymphomatoid papulosis and mycosis fungoides occurring in the same patients suggests a common origin. Hum Pathol. 2015; 46: 558-569.
5. Sanchez NP, Pittellow MR, Muller SA, Banks PM, Winkelmann RK. The clinicopathologic spectrum of lymphomatoid papulosis: study of 31 cases. J Am Acad Dermatol. 1983; 8: 81-94.
6. Cardoso J, Duhra P, Thway Y, Calonje E. Lymphomatoid papulosis is type D: a newly described variant easily confused with cutaneous aggressive CD8-positive cytotoxic T-cell lymphoma. Am J Dermatopathol. 2012; 34: 762-765.
7. McCurdy O, McCormack C, Ritchie D, Prince HM. Exacerbation of lymphomatoid papulosis during rituximab therapy. Australas J Dermatol. 2014; 55: e1-3.
8. Samaranwera AP, Cohen SN, Akay EM, Evangelou N3. Lymphomatoid papulosis: A cutaneous lymphoproliferative disorder in a patient on hormone-replacement therapy. Clin Exp Dermatol. 2009; 34: 635-636.
9. Spires N, McGibbon D. Lymphomatoid papulosis improving on hormone-replacement therapy. Clin Exp Dermatol. 2009; 34: 635-636.
10. Wong HK, Mishra A, Hala T, Porcu P. Evolving insights in the pathogenesis and therapy of cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome). Br J Haematol. 2011; 155: 150-166.
11. Eninga EA, Holtan SG, Creedon DJ, Dronca RS, Nevala WK, Ognjanovic S1, et al. Immunomodulatory effects of sex hormones: requirements for pregnancy and relevance in melanoma. Mayo Clin Proc. 2014; 89: 520-535.
12. Schumacher A, Costa SD, Zenzchusen AC. Endocrine factors modulating immune responses in pregnancy. Front Immunol 2014; 5: 196.
13. Mor G. Immunology of pregnancy. 2006.