

## Case Report

# Methotrexate-associated primary cutaneous CD30-positive cutaneous T-cell lymphoproliferative disorder: a case illustration and a brief review

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**Abstract:** Methotrexate (MTX) is a commonly used anti-metabolite agent. Increased risk of lymphoproliferative disorders (LPD) in patients with rheumatoid arthritis (RA) has been documented with the prolonged use of immunosuppressive medications such as MTX. This is thought to be the result of immune dysregulation and/or chronic immune stimulation. Most cases of LPDs regress following withdrawal of the offending immunosuppressive agent. We present an interesting and rare case of CD30 and EBV positive CD8 primary cutaneous anaplastic large cell lymphoma (PC-ALCL) in a 66-year-old African American woman. Patient had been on MTX for rheumatoid arthritis (RA) which was stopped after the patient was evaluated at our institution. Patient had an incredible response to stopping immunosuppression with spontaneous regression of skin lesions and disappearance of clonal malignant cell population as evidenced on serial biopsy specimens. Primary cutaneous CD30+ LPDs constitute about 30% of the primary cutaneous T-cell lymphomas (CTLs) and includes entities such as lymphomatoid papulosis (LyP), primary cutaneous anaplastic large cell lymphoma (PC-ALCL) and other CD30+ borderline LPDs. Histopathological criteria in addition to CD30 positivity is important for identification of these conditions. Treatment options include “wait and see”, phototherapy, radiotherapy, topical agents, systemic therapy and surgical resection. Prognosis is excellent and most cases resolve spontaneously on withdrawal of immunosuppression. Refractory cases may require aggressive local treatment or systemic therapy. Brentuximab Vedotin, an anti-CD30 antibody drug conjugate (ADC), may provide additional therapeutic option in refractory cases.

**Keywords:** Methotrexate, lymphoproliferative disorders

## Introduction

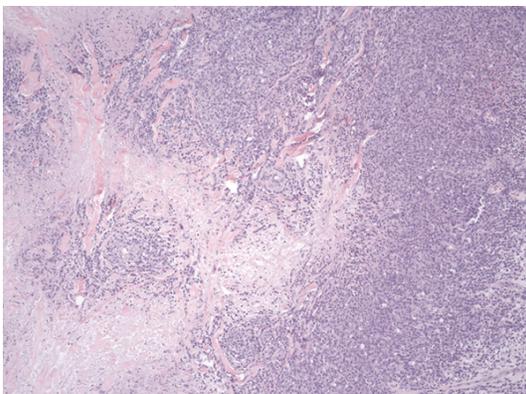
Anti-metabolite agent, methotrexate (MTX) is widely used for treatment of a myriad of conditions ranging from auto-immune diseases to malignancies. Case-controlled studies have shown an increased risk of lymphoproliferative disorders (LPD) in patients with rheumatoid arthritis (RA) when treated with prolonged use of immunosuppressive medications such as MTX [1]. Patients with auto-immune diseases inherently carry a high risk of LPD; however, this risk is further amplified by the use of immunosuppressive agents [2]. Higher incidence of non-melanoma skin cancers have been observed in RA patients on MTX [3]. This heightened risk of malignancy is believed to be linked to immune dysregulation and/or chronic im-

mune stimulation [2, 3]. Interestingly, the majority of the MTX-associated LPD are of B-cell origin, suggesting that MTX likely affects the B cell compartment more selectively [1, 4]. Nonetheless, MTX-associated cutaneous T-cell related LPD has been reported [5]. A number of anecdotal reports have described the development of a T-cell epidermotropic LPD in patients taking oral low-dose MTX, occasionally related to reactivation of latent Epstein Barr Virus (EBV) infection [3, 6, 7]. Interestingly, in most of these cases, LPD regresses upon withdrawal of the offending drug [4]. We report a case of an elderly African American woman with RA who developed a biopsy-proven CD30+ cutaneous LPD while on MTX and, subsequently had a complete regression upon MTX discontinuation.

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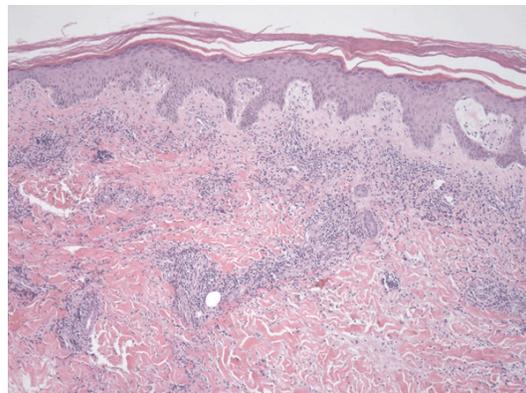
**Figure 1.** Left leg ulcerated lesions at initial presentation.



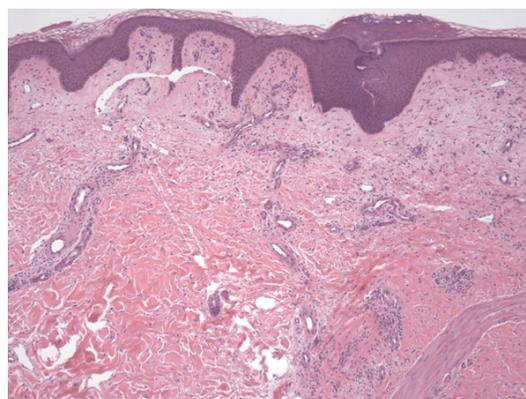
**Figure 2.** H&E (100X). First biopsy of the lesions showing diffuse lymphocytic proliferation with focal necrosis.

### Case report

A 66-year-old morbidly obese African American woman with a past medical history of diabetes mellitus type II, RA on treatment with MTX, hypertension, pulmonary hypertension and kappa light-chain restricted monoclonal gammopathy of unknown significance (MGUS) presented to our institution in November 2014 for evaluation of an ulcerated cutaneous lesions over her left leg (**Figure 1**). Biopsy of this lesion performed at an outside facility was compatible with EBV-related CD30+ T-cell LPD (**Figure 2**). These lesions were first noticed by the patient in September 2014 as small erythematous macular lesions. The lesions continued to gradually increase in size over the next few weeks which prompted the patient to seek medical attention.



**Figure 3.** H&E (100X). Second biopsy of the lesions showing dermal edema with lymphocytic proliferation centered around dermal vasculature and adnexal structures.



**Figure 4.** H&E (100X) Third biopsy of the lesion showing resolving lymphocytic proliferation.

The cutaneous lesions were initially treated as erythema-nodosum with antibiotics. When it failed to resolve, a punch skin biopsy was performed on October 10<sup>th</sup> 2014 and was reviewed in consultation with the Cleveland Clinic. Immunohistochemistry (IHC) demonstrated strong CD3 expression, with the majority of cells expressing CD8 phenotype. CD30 was diffusely expressed. CD20, CD56 and anaplastic lymphoma kinase (ALK) expression were immunonegative. EBV-encoded RNA (EBER) in situ hybridization (ISH) was positive. The cells also expressed cytotoxic proteins such as perforin, granzyme B and T-cell intracellular antigen-1 (TIA-1). Bone marrow biopsy was unremarkable for lymphoma involvement. Flow cytometry analysis on bone marrow was unrevealing. Cytogenetics showed a normal 46 XX karyo-

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**Table 1.** Categorization of T cell lymphoproliferative disorders

	Indolent	Aggressive
1	Mycosis fungoides	Sézary syndrome
2	Mycosis fungoides variants and subtypes	Adult T-cell leukemia/lymphoma
3	Primary cutaneous CD30+ lymphoproliferative disorder (eg, primary cutaneous anaplastic large cell lymphoma, lymphomatoid papulosis)	Extranodal NK/T-cell lymphoma, nasal type
4	Subcutaneous panniculitis-like T-cell lymphoma	Primary cutaneous peripheral T-cell lymphoma, unspecified
5	Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma	Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)
6		Cutaneous gamma/delta-positive T-cell lymphoma (provisional)

type with no chromosomal abnormalities. Computerized-tomography (CT) of the chest, abdomen and pelvis did not show any evidence of systemic involvement by lymphoma.

Taking in to account the localized nature of the patient's lesions and history of exposure to MTX, we decided to hold MTX and observe the patient closely. Subsequently, the patient started to notice healing and improvement of the skin lesions. A second skin biopsy was then performed on November 17<sup>th</sup>, 2014, approximately three weeks after stopping MTX. This showed the presence of large atypical lymphoid cells around blood vessels, but no diffuse growth pattern seen (**Figure 3**). EBER ISH was negative and the large lymphoid cells were immunonegative for CD30. The lesions continued to regress as evidenced on clinical examinations. A third skin lesion biopsy was performed approximately two months after stopping MTX. On this biopsy, small mature-appearing lymphocytes with no atypical large cells were observed (**Figure 4**). CD30 expression and EBER ISH were negative.

### Discussion

The majority of primary cutaneous lymphomas are of T-cell origin (9). T-cell associated LPDs include MF (roughly 70%) followed by CD30+ LPDs and others rare variants (**Table 1**). CD30 is a member of the tumor necrosis factor receptor (TNF) receptor superfamily. It has a variable expression in a number of lymphoid malignancies, benign lymphoproliferative processes and some inflammatory and allergic conditions [8].

Primary cutaneous CD30+ LPDs constitute about 30% of the primary cutaneous T-cell lymphomas (CTLs) and encompass a broad spectrum of entities with variable clinical course such as lymphomatoid papulosis (LyP), primary

cutaneous anaplastic large cell lymphoma (PC-ALCL) and other CD30+ borderline LPDs [9]. Many experts now believe that LyP and PC-ALCL are diseases on the same spectrum with PC-ALCL presenting as a single nodule and LyP with diffuse papulosis. However, overlapping clinical features are not uncommon. Morphologic criteria alone has been deemed to be insufficient to classify many cases of CD30+ LPDs. To complicate matters further, skin involvement may often times be a component of systemic manifestation of others non-Hodgkin Lymphomas (NHL) particularly mycosis fungoides (MF), lymphomatoid drugs reactions or cytotoxic T-cell lymphomas [10, 11].

EBV has been implicated as one of the causes of CD30+ LPDs arising in the post-transplant setting, in association with immunosuppressive drugs such as MTX or virus associated immunodeficiency (HIV). It is hypothesized that reduced immune-surveillance and/or chronic antigenic stimulation or a direct oncogenic trigger may be the underlying pathogenic process resulting in LPDs [1-4, 6, 7].

PC-ALCL commonly presents in adult males. Patients usually present with an isolated lower extremity nodule or papule that may ulcerate. However, about 20% of the patients may present with widespread lesions. In up to 25% of the patients, lesions regress spontaneously. Histopathological examination usually shows CD4 phenotype with expression of cytotoxic proteins such as granzyme B, perforin and TIA-1 and a preponderance of CD30+ anaplastic cells in the inflammatory background. ALK expression is not seen in PC-ALCL. T-cell receptor (TCR) gene rearrangement demonstrates clonality in majority of the cases. A complete imaging workup is recommended to rule out systemic lymphomatous involvement [9, 11-13]. A rarer entity, CD8+/CD30+ cutaneous

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LPDs constitutes only eight percent of the PC-ALCL cases. This presents with a significant diagnostic challenge, making it difficult to distinguish from primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, CD8+ gamma/delta or natural killer/T-cell lymphoma [9, 13, 14]. Solitary lesions are often treated by local excision or radiotherapy. MTX can be used for widespread lesions. Prognosis is usually excellent in majority of the patients with CD4 phenotype. However, epidermotropic CD8+ cytotoxic T-cell lymphoma is associated with a high risk of systemic dissemination and requires treatment with systemic chemotherapy [9, 11, 12].

LyP is a rare chronic recurring CD30+ LPD characterized by diffuse papulo-nodular eruption generally involving trunk and extremities. Lesions often times regress spontaneously resulting in complete resolution. This process usually follows a recurrent pattern over months or years. Even though LyP primarily affects the skin, it carries an increased lifetime risk of another LPD such as Hodgkin's lymphoma or MF [13]. On histopathological examination, these lesions may show a diverse background consisting of inflammatory cells, Reed-Sternberg like cells embedded with CD30+/- large cell (LyP type A, B, C). Prognosis is usually excellent except in few patients who may develop a second LPD. Treatment does not alter the natural course of the disease. Apart from a wait-and-see approach, MTX or phototherapy can be given for persistent and symptomatic lesions [9, 11, 12, 15].

Our patient case presented here is unique. It is a rare variant of CD30+ PC-ALCL with a predominant CD8 phenotype and EBV expression. The disease started in the presence of MTX and spontaneously resolved on MTX withdrawal. We hypothesize that the disease was the result of a "two hit" process. The "first hit" was the immunosuppression caused by MTX and the "second hit" resulted in virally-mediated oncogenic stimulation by EBV. These processes played a key role in clonal malignant transformation in this patient. Regression of the lymphomatous lesions upon discontinuation of MTX further supports the hypothesis that the mutual interaction of immunosuppression and oncogenic stimulation were necessary to initiate and sustain the malignant process. Also, in

contrast with the aggressive nature of the previously reported cases of CD8/CD30+ PC-ALCL, our patient had a benign course with spontaneous regression and no sign of disease recurrence till the date of this report.

CD30 is a cell surface glycoprotein that has pleiotropic effects on cell growth and survival. It is highly expressed in many LPDs including Hodgkin's lymphoma, ALCL and MF. The ubiquitous expression of CD30 in CTL makes it an excellent target for monoclonal antibodies and antibody-dependent cell-mediated cytotoxicity (ADCC) [8, 16]. Brentuximab Vendotin or Adcetris® is an antibody-drug conjugate (ADC) that targets CD30. This ADC comprises of an anti-CD30 monoclonal antibody attached by a protease-cleavable linker to a cytotoxic agent, monomethyl auristatin E (MMAE). Brentuximab Vendotin is FDA approved for salvage treatment of Hodgkin's lymphoma and systemic ALCL. Brentuximab Vendotin has shown strong activity in a recent study of 48 patients with CTL. Even though majority of the responses were in patients with MF, Brentuximab Vendotin also showed measurable clinical activity in a small group of patients with LyP and PC-ALCL [17].

### Conclusion

We present an interesting and rare case of CD30 and EBV positive CD8 PC-ALCL which arose in the setting of immunosuppression and spontaneously resolved after withdrawal of the offending agent, MTX. We show that after withdrawal of immunosuppression, the malignant clone spontaneously disappeared on biopsy specimens. This case teaches a valuable clinical lesson in recognition of LPDs associated with immunosuppression and subsequent treatment with mere withdrawal of the offending agent, thus, saving the patient from unnecessary treatment. Similar cases that fail to resolve spontaneously on withdrawal of immunosuppression can be possibly treated with new targeted agents like Brentuximab Vedontin.

### Disclosure of conflict of interest

William Tse, MD is a member of senior editorial board of American Journal of Blood Research.

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