Composite Cutaneous Lymphoma (Iatrogenic Immunodeficiency-Associated Lymphoproliferative Disorder) in a Patient with Rheumatoid Arthritis Treated with Methotrexate: Staging and Evaluation of Response to Therapy with ^{18}F -FDG PET/CT

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Abstract A 67 year old woman with a 10 year history of rheumatoid arthritis (RA) treated with methotrexate and prednisone, presented with a 2 year history of worsening multiple cutaneous plaques of variable appearance. Two distinct skin lesions were biopsied to reveal a composite cutaneous lymphoma, possibly caused by long term methotrexate therapy. An [18F] fluoro-2-deoxy-D-glucose (^{18}F -FDG) positron emission tomography/computed tomography (PET/CT) was performed to stage the malignancy, and was later repeated to evaluate response to chemotherapy, which guided subsequent management. We present the PET/CT imaging findings of this very rare iatrogenic (methotrexate induced) immunodeficiency-associated lymphoproliferative disorder.

Keywords Composite lymphoma · Cutaneous lymphoma · Iatrogenic immunodeficiency-associated lymphoproliferative disorder · Methotrexate · PET/CT · Rheumatoid arthritis

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Introduction

Cutaneous lymphoma is the second most common subtype of extra-nodal lymphoma after the gastrointestinal tract, and represents approximately 2% of all lymphomas [1–3]. In rare cases, a lymphoproliferative malignancy can develop from simultaneous clonal expansion of two distinct cell populations within a single organ or tissue, and is termed “composite lymphoma”. Composite lymphoma of the skin, also known as composite cutaneous lymphoma, is extremely rare [4–6].

The estimated risk of lymphoma in patients with RA is approximately twice that of the general population [7]. Methotrexate is one of several disease-modifying anti-rheumatic drugs that are suspected of further increasing the risk of lymphoma in these patients. These lymphomas are termed “iatrogenic immunodeficiency-associated lymphoproliferative disorders” in the 2008 World Health Organization classification of lymphoid neoplasms [8, 9]. The use of ^{18}F -FDG PET/CT in the staging and follow-up of iatrogenic immunodeficiency-associated lymphoproliferative disorders has not been previously described in the literature. We present a case of composite cutaneous lymphoma in a RA patient on long term methotrexate. In this case, ^{18}F -FDG PET/CT was very useful in staging the disease, in evaluating response to chemotherapy, and in guiding further management.

Case Report

A 67 year old woman with a 10 year history of RA treated with methotrexate (at a dose of 15 mg weekly over a period of 6 years, and prednisone at a dose ranging between 5 and

20 mg per day for variable periods), presented with worsening multiple pruritic cutaneous plaques that had begun to appear 2 years previously. The plaques were located on her face in the left supraorbital region, lower abdomen and the left lower leg (Fig. 1a–c). On physical exam, there was no evidence of enlarged peripheral lymphadenopathy or hepatosplenomegaly. The patient was referred for a staging ^{18}F -FDG PET/CT after punch biopsies of the facial and left lower leg lesions revealed a lymphoproliferative disease.

An ^{18}F -FDG PET/CT (Discovery ST, GE Healthcare, Waukesha, WI, USA) was performed. An ^{18}F -FDG emission scan extending from the base of the skull to mid thighs was obtained approximately 60 min after intravenous injection of 8.1 MBq/kg of ^{18}F -FDG. Maximum intensity projection (MIP) images with left lateral views of the body are shown (Fig. 1d). The arrows show ^{18}F -FDG uptake in the cutaneous lesions seen in the photos of Fig. 1a–c: left supraorbital region with maximum standardized uptake value (SUV_{max}) of 1.8, and the left lower abdomen with SUV_{max} of 2.9. Additional views of the legs were acquired and showed lesions on the left anterolateral shin with SUV_{max} of 1.8 and superolateral left calf with SUV_{max} of 1.2 (Fig. 2c). Bone marrow involvement was not suspected on PET/CT, and a bone marrow core biopsy was negative. Immunohistochemical evaluation of the skin biopsies revealed an infiltrate of malignant pleomorphic B- and T-lymphoid cells compatible with a composite lymphoma characterized by a follicular type B-cell lymphoma (supported by presence of bcl-6, bcl-2, and CD10 markers), and a T-cell lymphoma CD30+ lymphoproliferative disorder with Pautrier's microabscesses indicative of mycosis fungoides, previously described in detail by Huwait et al. [1]. Methotrexate therapy was stopped and the patient was treated with six cycles of chemotherapy with cyclophosphamide, vincristine, prednisone, and rituximab (CVP-R regimen).

A follow-up ^{18}F -FDG PET/CT was performed approximately 3 months after the end of chemotherapy and showed

a mixed response to therapy. The lesion on the left side of the lower abdomen resolved completely on both PET and CT, as did the previously ^{18}F -FDG avid lesions in both lower legs (Fig. 2b, d). There were, however, several new ^{18}F -FDG avid subcutaneous lesions consistent with progression of disease (Fig. 3a, b), the most intensely ^{18}F -FDG avid being a right groin cutaneous nodule with SUV_{max} 9.5 (Fig. 3c–e), in addition to numerous new cutaneous and subcutaneous lower abdominal (SUV_{max} 3.7), left flank (SUV_{max} 2.8), left upper chest wall (SUV_{max} 1.7), and scalp lesions (SUV_{max} 1.5). A scalp lesion in the left posterior auricular region was biopsied and showed a clonal population of CD30+ T-lymphocytes consistent with cutaneous T-cell lymphoma, without immunohistochemical or molecular evidence of a residual B-lymphocyte clonal population (Fig. 4). The B-cell component of the patient's composite cutaneous lymphoma was no longer detectable. Because of the suspected overall progression of the T-cell lymphoma component, the patient's therapeutic regimen was modified and the patient received additional treatments with alemtuzumab, total skin electron irradiation, UVB/PUVA light therapy, and bortezomib.

Discussion

Cutaneous lymphoma is the second most common subtype of extra-nodal lymphoma after the gastrointestinal tract and represents approximately 2% of all lymphomas [1–3]. The majority of cutaneous lymphomas are T-cell in origin, most often mycosis fungoides [2]. Clinical presentation of skin lesions may include papules, patches, plaques, tumors, with or without pruritus, and ulceration [3]. Rarely, a lymphoproliferative malignancy will develop from simultaneous clonal expansion of two distinct cell populations within a single organ or tissue, termed composite lymphoma, which can arise from B cells, T cells, NK cells, or a combination thereof [4, 5]. The incidence

Fig. 1 A 67 year old woman with a 10 year history of rheumatoid arthritis treated with methotrexate, who presented with multiple worsening pruritic cutaneous plaques on (a) the face in the left supraorbital region, (b) lower abdomen and (c) left lower leg (arrows).

(d) ^{18}F -FDG PET/CT MIP image with left lateral view of the body shows the ^{18}F -FDG avid lesions in the left supraorbital region and lower abdomen (arrows)

Fig. 2 Transaxial views of the PET and CT portions of the PET/CT show the left lower abdominal lesion (**a**) prior to chemotherapy and its complete metabolic resolution on a (**b**) PET/CT done 3 months after chemotherapy.

(**c**) The pre-chemotherapy ^{18}F -FDG positive lower leg lesions seen on MIP images (*arrows*) also show complete metabolic resolution on (**d**) PET/CT MIP images done 3 months after chemotherapy

of composite lymphoma involving the skin is exceedingly rare, estimated at only 1% of all cutaneous lymphomas [6].

The estimated risk of lymphoma in patients with RA is approximately twice that of the general population [7]. Furthermore, it has been postulated that methotrexate, among other disease-modifying anti-rheumatic drugs, independently increases the risk of lymphoma especially in the setting of a latent Epstein-Barr viral (EBV) infection [8, 9]. These are termed “iatrogenic immunodeficiency-associated lymphoproliferative disorders” in the 2008 World Health Organization classification of lymphoid neoplasms [1]. Our patient had

tested negative for EBV and partially responded to methotrexate withdrawal and six cycles of chemotherapy with CVP-R, with regression of the B-cell component and progression of the T-cell component. Although no conclusive evidence exists to validate a causal relationship between methotrexate therapy and the development of lymphoma, the most compelling data to corroborate this postulate was reported by Kamel et al. after spontaneous remission following methotrexate withdrawal [10]. Ichikawa et al. also reported spontaneous remission following methotrexate withdrawal in one of two composite lymphoma patients [11].

Fig. 3 Post chemotherapy PET/CT MIP images with (**a**) anterior and (**b**) lateral views of the body show several new ^{18}F -FDG avid cutaneous lesions consistent with progression of malignancy (*arrows*). Post chemotherapy transaxial (**c**) CT, (**d**) PET, and (**e**) PET/CT fusion images show a new cutaneous right groin nodule with SUV_{max} 9.5 (*arrow*)

Fig. 4 (a) Biopsy of a new scalp lesion in the left posterior auricular region showing intact epidermis with lymphocyte proliferation in the dermis. (b) High power view shows perivascular infiltrate by a small monotonous lymphocytic population. (c) There is no expression of the lymphocytes for CD20 (B-cell marker). (d) Strong and diffuse expression of the lymphocytes for CD5 (T-cell marker), consistent with a T-cell lymphoma

The use of ^{18}F -FDG PET/CT in the evaluation of composite cutaneous lymphoma, or any iatrogenic immunodeficiency-associated lymphoproliferative disorder (in this case, methotrexate induced), has not been previously described in the literature. The use of PET/CT in the evaluation of cutaneous lymphomas is controversial with studies often showing conflicting results. It appears that the usefulness of ^{18}F -FDG PET/CT depends on the histological subtype and aggressiveness of the particular cutaneous lymphoma being evaluated [12–17]. In this case, ^{18}F -FDG PET/CT was useful during staging by determining the extent of metabolically active malignant disease (with elevated ^{18}F -FDG uptake in clinically confirmed cutaneous lesions), and was also useful in evaluating response to chemotherapy by showing regression of some lesions and progression of others (with histological evaluation confirming regression of the B-cell component and progression of the T-cell component), which resulted in a significant change in the patient's subsequent management.

Compliance with Ethical Standards

Conflict of Interest William Makis, Anthony Ciarallo, Beatrice Wang, Milene Gonzalez-Verdecia and Stephan Probst declare that they have no conflict of interest.

Ethical Statement The study was approved by an institutional review board or equivalent and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All subjects in the study gave written informed consent or the institutional review board waived the need to obtain informed consent.

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