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Primary Cutaneous Peripheral T-Cell Lymphoma-Not Otherwise Specified, Initially Misdiagnosed as Mycosis Fungoides: A Case Report and Literature Review

Zara Saeed[1*], Humaira Talat[2], Reema Mirza[3], Zuha Saleem[4]

[1,2,3,4]Department of Dermatology, Dow University of Health Sciences, Pakistan

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***Correspondence:**
zarasaeed29@gmail.com

ABSTRACT

This report describes the case of a 52-year-old male who presented with a four-month history of multiple hyperpigmented lesions, predominantly affecting the trunk and upper limbs. On physical examination, numerous hyperpigmented patches and plaques were observed, with the largest lesion located on the right flank. Systemic examination revealed hepatomegaly, splenomegaly (tip of the spleen palpable), and right inguinal lymphadenopathy. The patient had no history of fever, weight loss, or other chronic illness. Initially, he was labelled as a case of mycosis fungoides; however, a repeat cutaneous biopsy, along with a lymph node biopsy, established the diagnosis of Primary Cutaneous Peripheral T-Cell Lymphoma – Not Otherwise Specified (pcPTCL-NOS). The patient was treated with six cycles of the CHOP regimen, resulting in initial resolution of the lesions. A post-chemotherapy PET scan showed no evidence of residual disease. This case emphasizes the importance of a comprehensive clinical evaluation, as the patient's acute history and systemic involvement hinted towards a far more aggressive disease process. Through a series of investigations, the correct diagnosis was made, facilitating the timely initiation of appropriate management.

Primary Cutaneous Peripheral T-Cell Lymphoma – Not Otherwise Specified (pcPTCL-NOS) is a rare and heterogeneous form of cutaneous lymphoma, representing a subset of primary

cutaneous T-cell lymphomas (CTCL) that do not meet the criteria for any of the recognized histopathological subsets [1]. The clinical presentation of pcPTCL-NOS is highly variable as it may manifest as solitary or multiple nodules, plaques or tumors [2]. The lesions may become ulcerated and rapid systemic involvement often ensues [2]. Therefore, these tumors are most often misdiagnosed leading to delays in treatment. These tumors are highly aggressive, with a poor treatment response and grave prognosis [1]. This case report describes the diagnostic challenge faced by a 52-year-old male, who was initially misdiagnosed with mycosis fungoides, and eventually identified as a case of pcPTCL-NOS. This highlights the significance of a thorough clinical and histopathological evaluation when confronted with such atypical cutaneous presentation, a rapidly progressing disease process and potential systemic involvement.

Case Presentation

A 52-year-old male with no known co-morbidities, presented with a four-month history of multiple dark-colored lesions primarily affecting his trunk and limbs. The lesions began as small, red, raised patches and plaques on his trunk, which progressively increased in number, enlarged and became hyperpigmented. They were associated with mild itching; however, the patient denied any history of fever, weight loss or night sweats.

Cutaneous examination revealed multiple light to dark brown, hyperpigmented patches and plaques of irregular shapes and sizes, predominantly affecting the trunk and upper limbs, with sparing of the face, scalp, palms, and soles (Figure 1). The largest lesion, measuring 11x6 cm, was located on the right flank (Figure 2). It was indurated, non-tender, mildly warm to the touch, and had overlying wrinkling with fine, dry white scales. A single, non-tender, mobile lymph node, measuring 2x1.5 cm, was palpated in the right inguinal region, without fixation to underlying structures. The liver was palpable three finger breadths below the right costal margin, with a liver span of 16 cm. The tip of the spleen was also palpable.

Figure 1. Cutaneous examination revealed multiple hyperpigmented patches and plaques of different shapes and size.

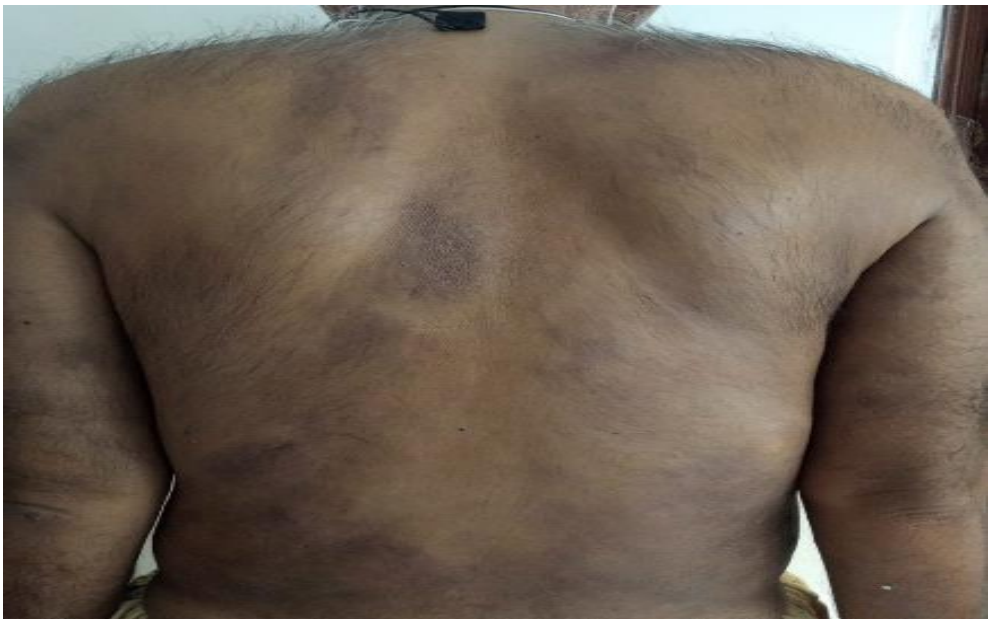
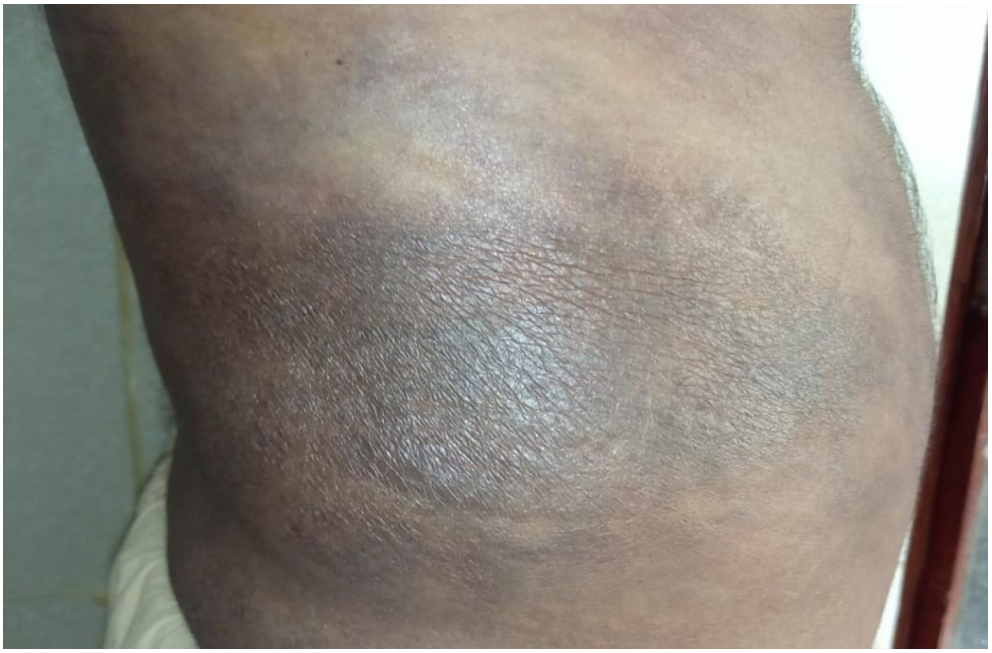


Figure 2. The largest plaque was present in the right flank area, having dry, wrinkly surface with fine white scales.



Laboratory workup revealed a hemoglobin level of 9 g/dL (13-16mg/dL) and a total leukocyte count (TLC) of 2.8 x 10^3/µL (4-11 x 10^3/µL). Given the bicytopenic picture on the CBC, further investigations were done. The lactate dehydrogenase (LDH) level was elevated at 3879 IU (105-233 U/L), with a reticulocyte count of 2.42% (0.5%-2.5%). The peripheral smear revealed normochromic, normocytic anemia with anisocytosis, which was consistent with bicytopenia. The initial skin biopsy revealed nodules of atypical lymphoid cells in the deeper dermis and subcutaneous tissue, characterized by enlarged, rounded nuclei with prominent nucleoli and scant cytoplasm, surrounding the adnexal structures. Foci of apoptosis and necrosis were also observed. Immunohistochemical analysis showed positivity for LCA and CD3 in large cells, while CD4 showed focal positivity. CD8, CD20, ALK1, and CD30 were all negative, while Ki-67 was positive in 90% of the tumor cells. A diagnosis of mycosis fungoides was given; however, the absence of epidermotropism and other characteristic histological features, along with a short disease duration of four months, incited further investigation.

CT imaging of the chest, abdomen, and pelvis revealed bilateral multifocal infiltration involving the skin, subcutaneous tissue, and musculature, affecting the anterior, lateral, and posterior chest and abdominal walls. Hepatosplenomegaly and bilateral subcentimetric axillary and superior mediastinal lymphadenopathy was noted alongside enlarged inguinal lymph nodes, predominantly on the right side, with the largest node measuring 2.0 x 1.8 cm. These findings were suggestive of a diffuse infiltrative process, most likely lymphoma.

Given the high clinical suspicion, a repeat skin biopsy and a CT guided right inguinal lymph node biopsy were performed. The skin biopsy showed atypical, medium-sized lymphoid cells with inconspicuous nucleoli and amphophilic cytoplasm, present in the deep dermis, subcutis, and vessel lumens, with evidence of apoptosis. The lymph node biopsy revealed fibrocollagenous stroma with crushed lymphoid cells and dilated vessels containing similar atypical cells. Immunohistochemistry revealed positive staining for Pan T (CD3), with reduced CD5, CD4, and CD8 expression. CD34, TdT, CD20, CD30, BCL-2, Mum-1, BCL-6, CD10,

EBV, and CD56 were negative. Ki-67 was positive in 80-90% of cells. These findings were consistent with high-grade T-cell lymphoma, favoring Primary Cutaneous Peripheral T-Cell Lymphoma, Not Otherwise Specified (pcPTCL-NOS).

Hematology and oncology were taken on board, and a bone marrow biopsy was performed. The bone marrow biopsy revealed bicytopenia and showed 40-50% cellularity with areas of abnormal lymphoid cell infiltration. The patient was identified as having advanced **Stage III** disease, characterized by widespread cutaneous involvement, lymphadenopathy, and hepatosplenomegaly. Treatment with a **CHOP regimen** (cyclophosphamide, doxorubicin, vincristine, and prednisone) was started, and the patient underwent six cycles of chemotherapy. Post-chemotherapy **CT** showed partial resolution of skin lesions, and **PET scan** revealed no residual disease, indicating a positive response to treatment.

Discussion

According to the WHO-EORTC classification of cutaneous lymphomas, pcPTCL-NOS is a diverse group of aggressive tumors that do not identify with any of the other well defined subtypes of cutaneous T cell lymphomas [1]. They account for around 2% of the primary CTCLs and have a 5-year survival of 15% [3]. It is usually seen in the adult population, predominantly in men and usually presents in the sixth to seventh decade [4]. A causal relationship with smoking, immunosuppression, pesticides and EBV has been proposed but is not explicitly defined [4].

The clinical presentation is highly variable and may mimic other plaque like conditions. It usually presents with single or multiple plaques or nodules, which may be localized or multifocal [3]. Disseminated disease involving the trunk and extremities has been defined as the most common presentation in a multicenter EORTC cutaneous lymphoma taskforce study [5]. This identifies with the pattern seen in our patient. Generalized lymphadenopathy as well as extranodal disease involving the liver, spleen and bone marrow, is frequently seen. B symptoms and pruritus are more common with systemic involvement. Laboratory abnormalities might include mild anemia, thrombocytopenia, hypereosinophilia and a raised LDH level [4]. It is a very aggressive tumor, with the majority of the patients presenting with advanced (stage III-IV) [6].

Skin lesions may show diffuse, nodular, or band like pattern of infiltrate predominantly involving the dermis. There is usually no or mild epidermotropism [5]. The infiltrate is composed of atypical lymphocytes with cells ranging from medium to large size, having round, oval or irregular nuclear contours with vesicular chromatin [7]. Immunohistochemistry panel is usually positive for pan T-cell markers – CD2, CD3, CD4, with loss of CD5, CD7 and CD30. Aberrant phenotypes are occasionally seen. This is accompanied by a high proliferation index Ki-67 up to 90% - representing the aggressive nature of these tumors [8].

Management requires exhaustive investigations including lymph node biopsy, bone marrow biopsy, and preferably a PET scan to correctly stage the patient. Treatment regimens with multiagent chemotherapeutic agents are usually employed, the most common being the CHOP regimen [9]. Newer agents like rapamycin and brentuximab vedotin have been used with favourable outcomes [10, 11]. Despite the initial resolution of skin lesions, prognosis remains poor, with average disease-free survival of around 8 months for responders [12]. The disease course is aggressive and independent of initial presentation, age and phenotype [5].

Conclusion

This case highlights the diagnostic dilemma faced when dealing with pcPTCL-NOS, an entity that has a varied presentation and can masquerade as several other dermatological conditions. It is imperative for the dermatologist to keep a high degree of suspicion when dealing with cases where the given histopathological diagnosis is inconsistent with the clinically aggressive course of disease. Patients are often misdiagnosed initially, so multiple biopsies and extensive investigations may be required. An early diagnosis and prompt initiation of treatment is of paramount importance in such aggressive diseases and may help prolong survival.

Declarations

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Ethics Approval

Not applicable.

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