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# An Isolated Cutaneous Relapse in a Known Case of Systemic ALK-Positive Anaplastic Large Cell Lymphoma: A Rare Case Report with Review of Literature

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## Abstract

Among non-Hodgkin's lymphomas (NHLs), anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) is a relatively uncommon subtype that accounts for 3% of all adult NHLs. It typically affects young males, with a prevalence of three to one. Most cases present with nodal disease at the time of presentation. An extranodal involvement is seen in 60% of cases and skin involvement is seen in only 8 to 21% of cases. Cutaneous involvement in ALCL can manifest as primary cutaneous ALCL or secondary to systemic ALCL, and while CD30 positivity is common to both, ALK is not expressed by the former. A secondary skin involvement is usually associated with a poorer prognosis.

We report a rare case of an isolated cutaneous relapse of systemic ALK-positive ALCL in a 62-year-old woman following the second cycle of chemotherapy. The acute febrile, widespread papulonodular eruption clinically resembled mycosis fungoides and lymphomatoid papulosis. With the introduction of oral crizotinib, a drastic improvement in the skin lesions and an exceptional response on positron emission tomography-computed tomography were noted.

**Keywords**

- ALCL
- ALK-positive anaplastic large cell lymphoma
- ALK-positive ALCL
- cutaneous metastasis
- crizotinib

## Introduction

Anaplastic large cell lymphoma (ALCL), which makes up 2% of all non-Hodgkin's lymphoma (NHL) cases, is a relatively uncommon subtype of NHL. Among the nodal T cell lymphomas, it is the third most prevalent subtype observed in adults and the most common subtype observed in children.

Anaplastic lymphoma kinase (ALK)-positive ALCL is caused by a translocation of the ALK gene located on chromosome 2. Most cases present with nodal disease at the time of presentation. An extranodal involvement is seen in 60% of cases and skin involvement is seen in only 8 to 21% of cases.[1] A secondary skin involvement is usually associated with a poorer prognosis.[2]

We hereby report a rare case of systemic ALK-positive ALCL in a 62-year-old woman who presented with an isolated cutaneous relapse following the second cycle of chemotherapy.

## Case Report

A 62-year-old woman who was previously diagnosed with stage 4 systemic ALK-positive ALCL, presented to the

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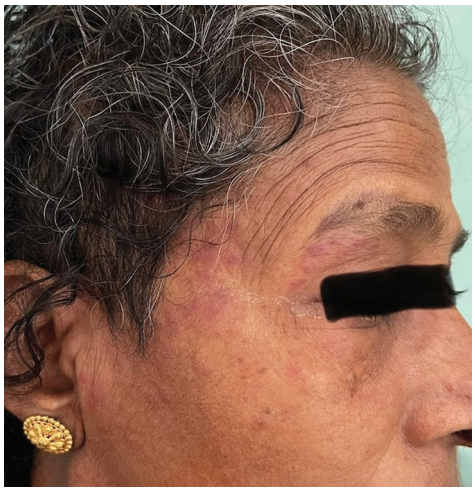

**Fig. 1** Asymptomatic skin lesions presented 2 weeks after second cycle of chemotherapy (day 1).

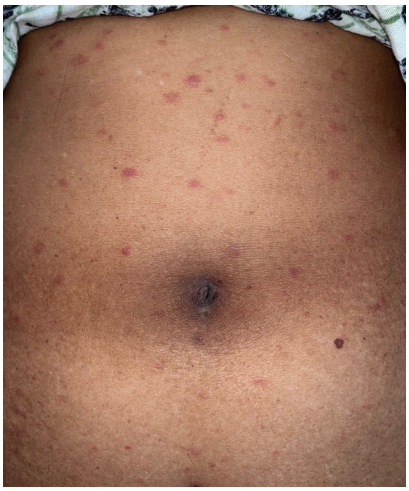

**Fig. 3** Asymptomatic skin lesions presented 2 weeks after second cycle of chemotherapy (day 1).

dermatology outpatient department with skin lesions 2 weeks after the second cycle of chemotherapy. She had completed two cycles of chemotherapy with subcutaneous filgrastim 300 mcg and intravenous infusion of vincristine 0.5 mg and cyclophosphamide 500 mg.

The skin lesions were multiple, asymptomatic, and initially started over the right zygoma of the face and right periorbital region and rapidly progressed downwards to involve the neck, chest, abdomen, back, bilateral thighs, and lower legs in that order (►**Figs. 1**–**3**). On examination, multiple pink to red papules, plaques, and nonindurated nontender nodules were noted. The lesions ranged from 3 mm to 1 cm in size and rapidly progressed over 4 to 5 days to become generalized and showed evolution through different stages of papule, nodule, and plaque. The patient had a history of fever 3 days prior, which was low grade and intermittent. Cutaneous T cell lymphoma and lymphomatoid papulosis (LyP) were among the differentials considered.

At the time of examination, blood pressure, respiratory rate, and pulse rate were within normal limits. General physical examination and systemic examination were not remarkable.

Laboratory evaluation revealed hemoglobin of 11.5 mg/dL and Total Leucocyte Count (TLC) of 11,390 cells/mm$^3$ with neutrophils being 82.1%. Peripheral smear showed normocytic normochromic anemia with neutrophilia. The erythrocyte sedimentation rate was raised at 90 mm/hour and C-reactive protein was elevated at 89 mg/L. Serum lactate dehydrogenase was raised at 212 U/L and serum calcium was decreased at 7.5 mg/dL. Tests for the malarial parasite, typhoid, dengue, and blood culture were negative, and other routine hematological and biochemical investigations were within normal limits. Sputum for acid-fast bacilli and real-time polymerase chain reaction by cartridge-based nucleic acid amplification test was negative for tuberculosis and infectious disease serology was also negative. Chest X-ray was reported normal and bone involvement was ruled out.

Biopsy from the right cervical lymph node revealed partial effacement of architecture by sheets of atypical lymphoid cells, which were large-sized with hyperchromic nuclei and prominent nucleoli (►**Fig. 4**). A few Reed–Sternberg-like cells and hallmark horseshoe-shaped cells were also noted

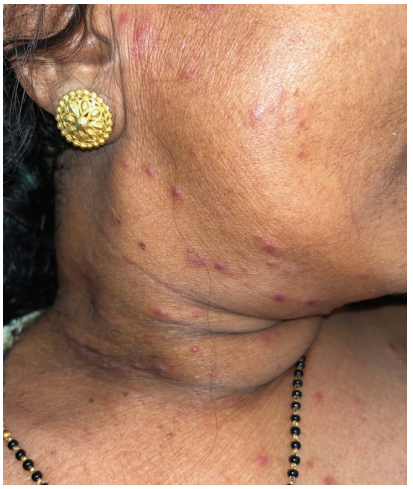

**Fig. 2** Asymptomatic skin lesions presented 2 weeks after second cycle of chemotherapy (day 1).

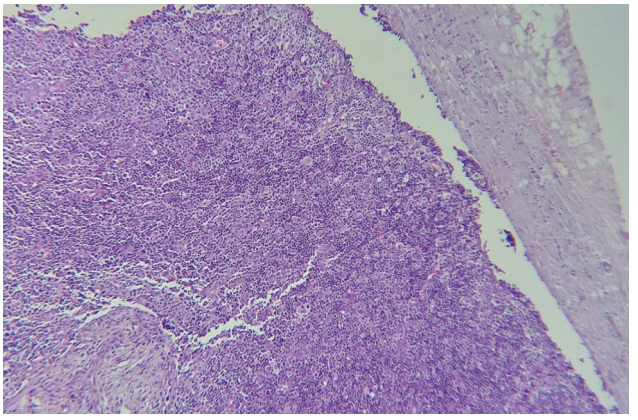

**Fig. 4** Right cervical lymph node biopsy shows effacement of architecture by sheets of lymphoid cells (hematoxylin and eosin [H&E], 10 ×).

 

(►**Fig. 5**). Immunohistochemistry (IHC) showed positivity for ALK and CD30 (►**Figs. 6** and **7**).

Skin punch biopsy was done from an erythematous papule over the abdomen and histopathological evaluation showed evidence of cutaneous metastasis with sheets of lymphoid cells in interstitial and angiocentric pattern with mildly enlarged nucleus and vesicular chromatin. There was an admixture of neutrophils and mitotic figures were also noted (►**Figs. 8** and **9**). IHC on the skin specimen showed positivity for ALK and CD30 (►**Figs. 10** and **11**).

Scanning with fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) showed increased FDG uptake in the cervical, mediastinal, axillary, and retroperitoneal lymph nodes with no extranodal involvement (►**Fig. 12**).

A diagnosis of isolated cutaneous relapse of systemic ALK-positive ALCL was established based on clinical, histopathological, IHC, and PET-CT findings.

The patient was started on tablet crizotinib 250 mg twice daily for 14 days and chemotherapy was withheld.

The skin lesions significantly improved following 10 days of treatment with oral crizotinib (►**Figs. 13**–**15**). The erythematous papules and nodules drastically resolved leaving behind hyperpigmented macules and some showed scarring with whitish atrophic centers. There was no new fresh crop of lesions. During the 6 months that the patient was monitored, no comparable relapse was noted (►**Figs. 16** and **17**). PET-CT done after 6 months showed hypermetabolic right hilar and paratracheal lymph nodes, likely lymphomatous involvement with no systemic involvement. Compared with the earlier scan, a near-complete metabolic response indicating an excellent response to crizotinib was noted (►**Fig. 18**).

## Discussion

In 1985, Stein et al initially described ALCL as a lymphoma characterized by large anaplastic lymphoid

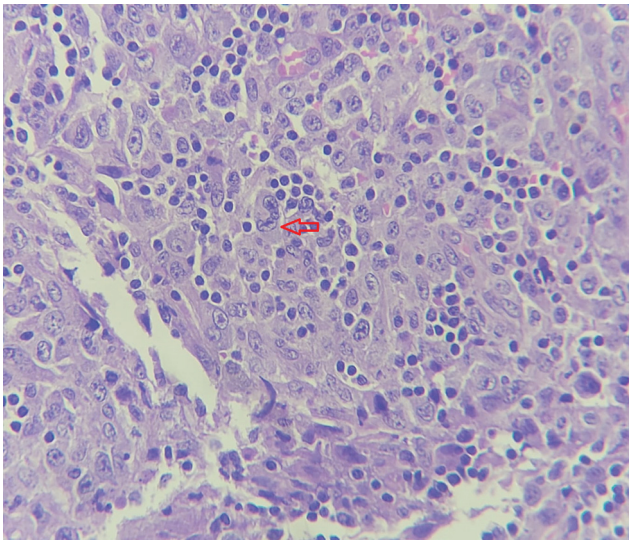

**Fig. 5** Red arrow shows hallmark horseshoe-shaped cells (hematoxylin and eosin [H&E], 40 ×).

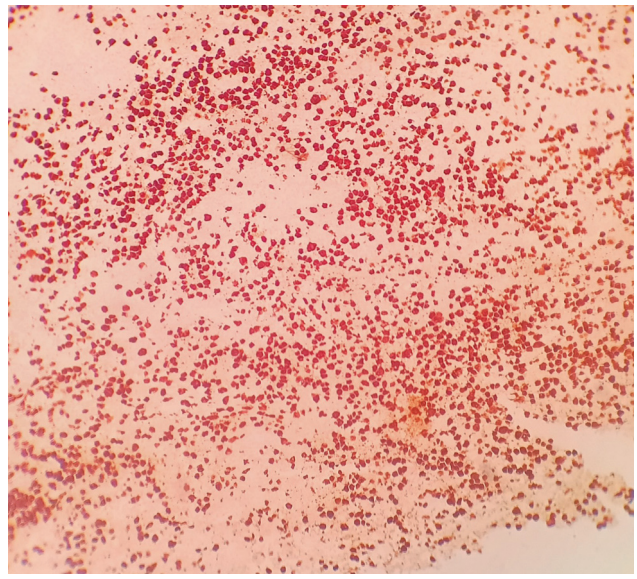

**Fig. 6** Right cervical lymph node biopsy showing anaplastic lymphoma kinase (ALK) positivity on immunohistochemistry (IHC).

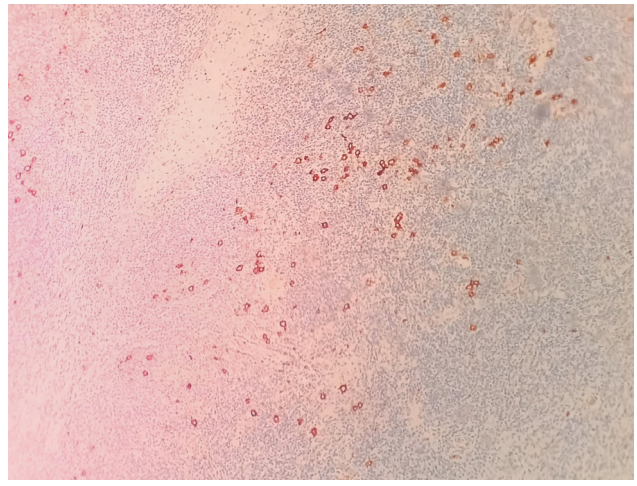

**Fig. 7** Right cervical lymph node biopsy showing CD30 positivity on immunohistochemistry (IHC).

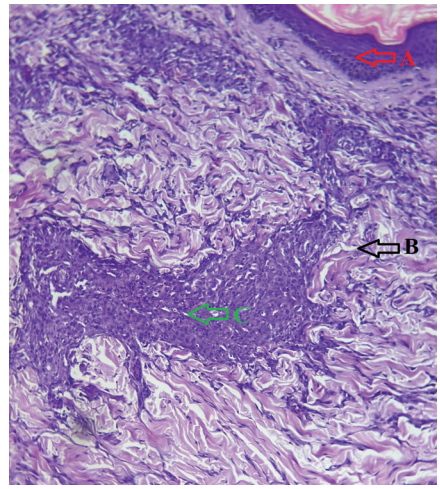


**Fig. 8** Skin biopsy from erythematous papule shows (**A**) epidermis, (**B**) dermis, and (**C**) sheets of lymphoid cells in the papillary and reticular dermis (hematoxylin and eosin [H&E], 10 ×).

 

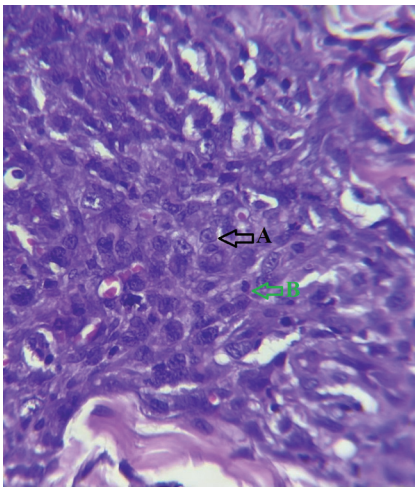


**Fig. 9** Skin biopsy shows (**A**) atypical lymphoid cells with an enlarged nucleus, vesicular chromatin, and ill-defined pale cytoplasm. (**B**) Mitotic figures (hematoxylin and eosin [H&E], 40 ×).

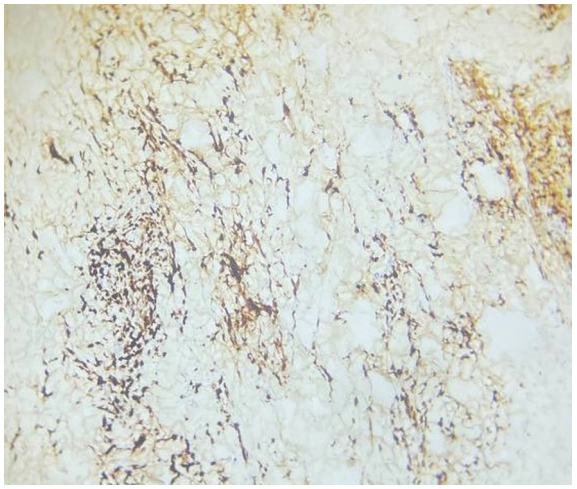

**Fig. 10** Skin biopsy showing cytoplasmic anaplastic lymphoma kinase (ALK) positivity on immunohistochemistry (IHC).

cells that were CD30-positive and had a propensity to invade lymph node sinuses and proliferate cohesively.[3]

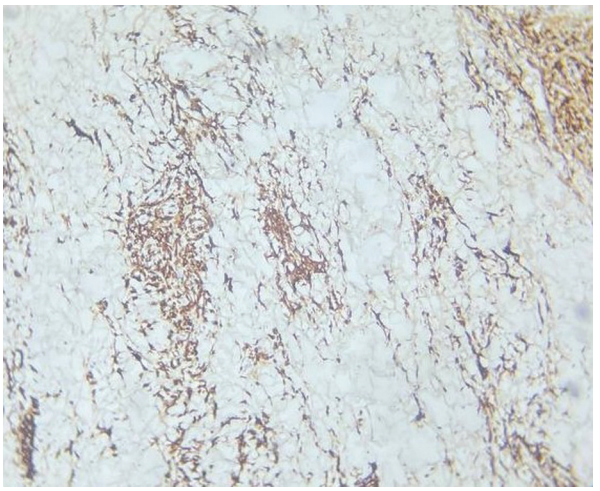

**Fig. 11** Skin biopsy showing cytoplasmic CD30 ($K_i$) positivity on immunohistochemistry (IHC).

Three types of ALCL are currently recognized by the World Health Organization, namely, primary cutaneous ALCL (PCALCL), ALK-positive ALCL, and ALK-negative ALCL.[4] While the last two types are systemic in nature, the first type manifests primarily in the skin.

About 3% of all adult NHLs and 10 to 15% of NHLs in children have been attributed to ALK-positive ALCL. It is distinguished by the NPM-ALK t(2; 5) translocation, which has a high correlation with the immunohistochemical detection of ALK protein.[5] It typically affects young males, with a prevalence of three to one. It usually presents as an advanced stage III to IV disease and is often accompanied by fever, which is caused by tumor cells releasing cytokines.[6]

ALK positivity is associated with a favorable outcome with an overall 5-year survival rate of 70 to 80% for ALK-positive ALCL and 33 to 49% for ALK-negative ALCL, respectively.[7] Despite being rare in adults, ALCL in the elderly is usually ALK-negative, contrary to our case.

Although it predominantly involves the lymph nodes, 45 to 60% of cases show extranodal involvement, presenting at a primary site or as a component of a systemic process. Skin

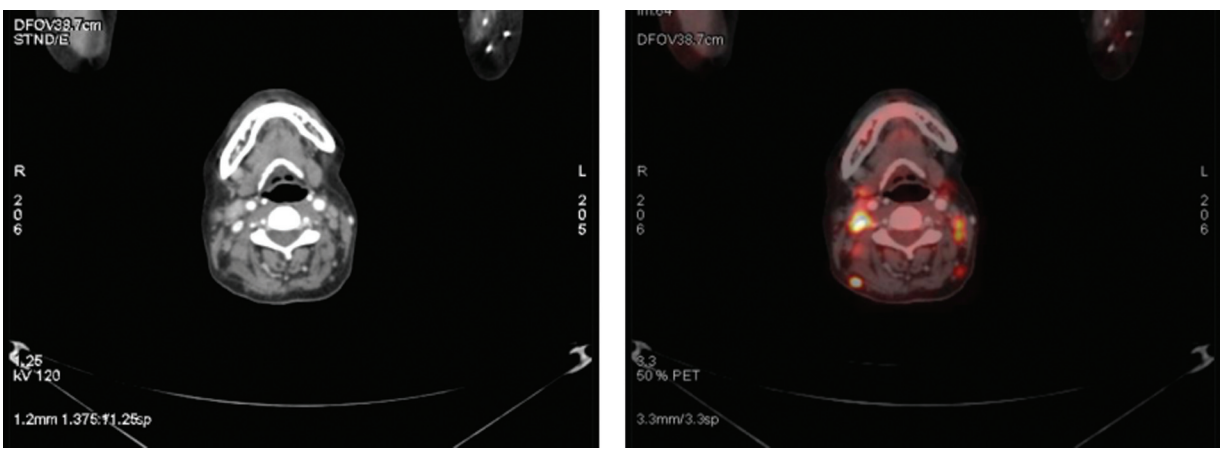


**Fig. 12** Positron emission tomography-computed tomography (PET-CT) showing increased fluorodeoxyglucose (FDG) uptake at the cervical lymph node.

 

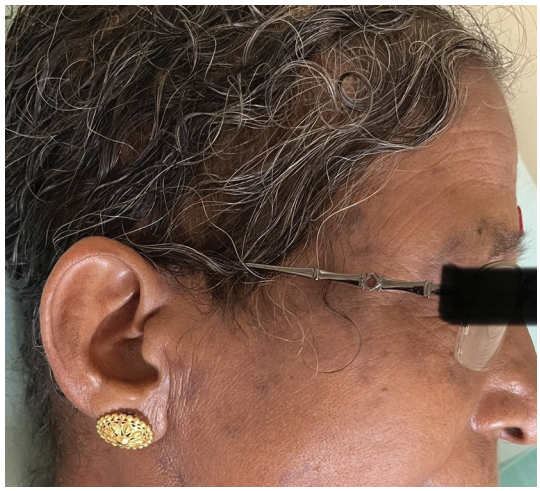

**Fig. 13** Healed skin lesions after treatment with crizotinib (day 10).

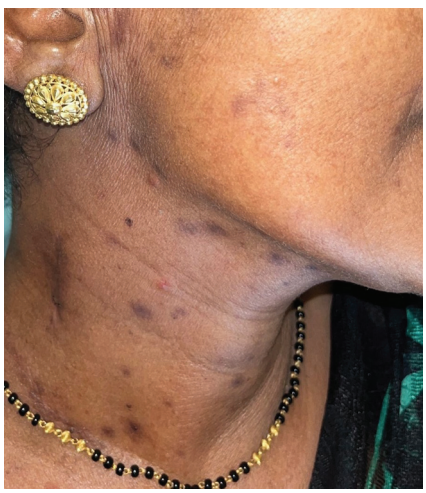

**Fig. 14** Healed skin lesions after treatment with crizotinib (day 10).

(15–30%), liver (5–10%), lung (5–15%), bone (5–20%), soft tissue (10–20%), and occasionally intestine and muscle are among the extranodal sites affected.[8]

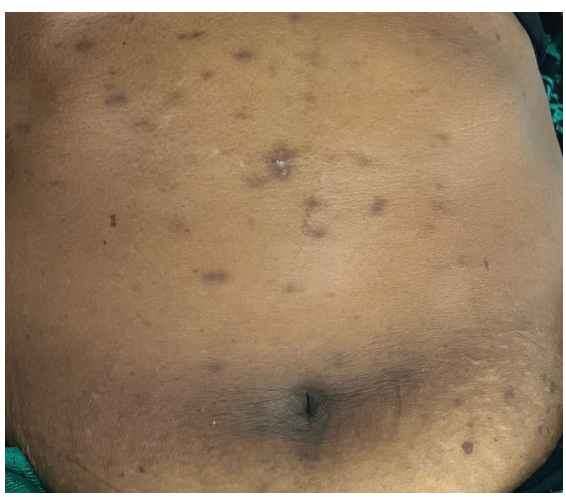

**Fig. 15** Healed skin lesions after treatment with crizotinib (day 10).

**Fig. 16** Sixth-month follow-up.

Secondary cutaneous involvement in ALK-positive ALCL needs to be differentiated from CD30-positive lymphoproliferative disorders (LPDs), namely, LyP and PCALCL, both of which exhibit the presence of CD30-positive neoplastic T cells similar to systemic ALCL, but lack ALK positivity. Since LPDs show an excellent prognosis, an overly aggressive treatment regimen should be avoided.[9]

PCALCL presents primarily as a large nonrelapsing solitary nodule that frequently ulcerates, and most commonly involves the head and extremities. It has a gradually progressive course and with a 90% 5-year survival rate, it shows an excellent prognosis after surgical excision without chemotherapy.[10]

Conversely, LyP is characterized by recurring, chronic, papulonodular skin lesions, which heal with hypopigmented or hyperpigmented scarring in 4 to 6 weeks. Lymphomas like mycosis fungoides (MF), Hodgkin's lymphoma, and ALCL can occur concurrently, before or after the occurrence of LyP. It has a chronic course and with a 5-year survival rate of nearly 100%, it shows a remarkable prognosis.[10]

With multiple asymptomatic erythematous papules, nodules, and plaques distributed across the body, our case's

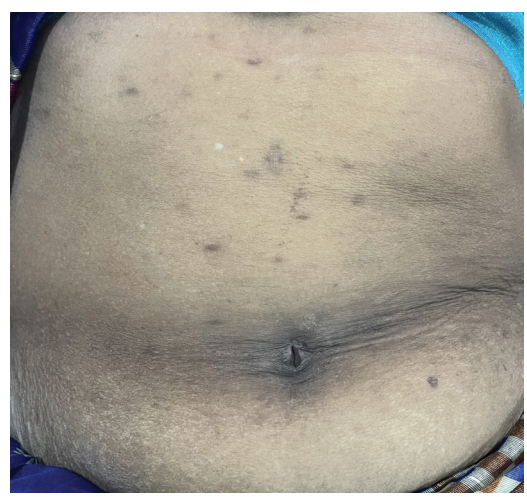

**Fig. 17** Sixth-month follow-up.

 

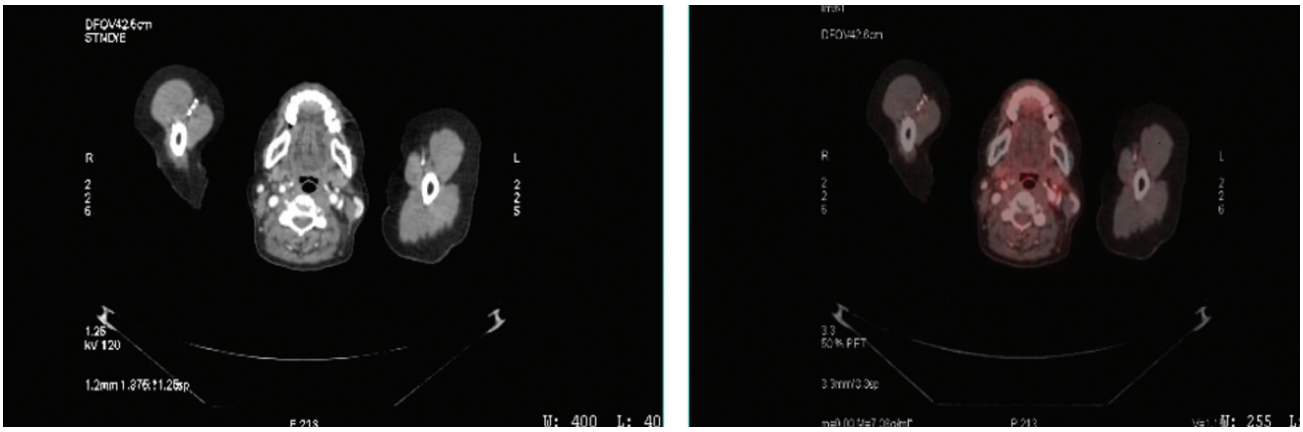

**Fig. 18** Positron emission tomography-computed tomography (PET-CT) after 6 months showing no abnormal fluorodeoxyglucose (FDG) uptake and a near-complete metabolic response at the cervical lymph node.

clinical appearance was similar to that of LyP; however, ALK positivity substantially ruled out the possibility of LyP.

Another differential to be considered is the papular form of MF (PMF). Clinically, PMF lesions are more homogenous and monomorphous and reappear in the future. Histology shows features of early MF and on IHC, CD30 negativity is seen in PMF. In our case, the lesions were polymorphous, did not recur in the future, and displayed CD30 positivity on IHC.[11]

For systemic ALCL, polychemotherapy is the preferred choice of therapy. The combination of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP regimen) or CHOEP regimen (CHOP plus etoposide) is typically used to treat patients with ALK-positive ALCL, and these anthracycline-based regimens offer a favorable prognosis. For ALK-positive ALCL, promising targeted treatment options include ALK inhibitors like crizotinib, ceritinib, and brentuximab vedotin, which is a monoclonal antibody directed against CD30-positive tumor cells.[1]

Our patient was diagnosed with a nodal ALCL-type NHL in the cervical lymph node, and later reported an acute onset of febrile papulonodular lesions. Although ALCL is more common in young males, in our case the subject was an elderly female in her sixth decade of life, who presented with advanced stage 4 disease. Despite the differentials considered, CD30 positivity ruled out PMF, while ALK positivity ruled out LyP and PCALCL. Immunohistochemical detection of ALK is highly likely to be a cutaneous manifestation of an underlying systemic ALCL,[12] which correlates with our case. Other extranodal site involvement was ruled out through PET-CT and skin biopsy provided substantial evidence, pointing toward a final diagnosis of an isolated cutaneous relapse of systemic ALK-positive ALCL.

In our case, although chemotherapy was initiated, a poor patient response was noted. Due to poor prognostic factors such as advanced age, female sex, and secondary skin involvement, chemotherapy was eventually discontinued and the patient was subsequently started on a targeted ALK inhibitor, crizotinib. With the introduction of crizotinib, a drastic improvement in skin lesions with no subsequent cutaneous relapse over 6 months and a near-complete metabolic response on PET-CT indicating an excellent response to the drug was noted.

An isolated cutaneous involvement was reported in the context of systemic ALK-positive ALCL. Although skin involvement in systemic ALCL is seen in 15 to 30% of cases, it is most commonly seen in pediatric and young adults with other extranodal site involvement, whereas in our case the subject was an elderly female with no other systemic involvement clinically and on imaging. Although clinically the lesions resembled LyP at presentation, on IHC all the differentials including LyP, PCALCL, and PMF were ruled out. After taking oral crizotinib, skin lesions tremendously improved and healed in 10 days. There was no subsequent cutaneous relapse over 6 months and PET-CT established the excellent effectiveness of the drug.

Mendiratta et al[13] reported papulonodular eruption in a 7-year-old boy, while Murkute et al[14] reported an indurated plaque studded with nodules in a 28-year-old woman, in the background of systemic ALCL. With not many similar cases reported in the literature, our case of systemic ALK-positive ALCL with an isolated cutaneous relapse in an elderly female is worthy of interest.

### Declaration of the Patient Consent form

Written informed consent was obtained from all the patients and/or guardians.

### Conflict of Interest

None declared.

### Acknowledgment

None.

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