

## Long-standing CD4+ /CD8+ Woringer-Kolopp Disease: A Report of A Rare Case

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### ABSTRACT

**INTRODUCTION:** Woringer-Kolopp disease is a localized pagetoid reticulosis (PR). It is a very rare variant of mycosis fungoides (MF).

**CLINICAL CASE:** A 44-year-old Malay lady presented with intermittent pruritic erythematous papular lesions over the right for about 20 years but did not seek treatment. The lesion gradually increased in size and turned into a verrucoid plaque. Ultimately, it became ulcerated and is associated with foul-smelling pus discharge. On examination, a large, verrucous plaque (16cm) with ulceration and erosion on the right heel, extending to the lower calf is seen. No other cutaneous lesions are present. Systemic and lymph nodes examination are negative. Skin biopsy cultures and TB PCR are negative. HPE reveals neoplastic T-cells with cerebriform nuclei, perinuclear halo and nuclear pleomorphism confined to the epidermis. These cells are positive for LCA, CD3, CD4, CD5 and

CD8. Other relevant immunostains were negative. The proliferative index is high (> 80%). MRI of the right leg shows suspicious regional tendon involvement. Staging CT scan shows no disseminated disease. No atypical lymphocytes seen in peripheral blood smear. Infective screenings are negative.

**DISCUSSION:** PR is an indolent disease with excellent prognosis as opposed to primary cutaneous aggressive epidermotropic CD8+ T cell lymphoma (PACTL), its disseminated form. Histopathologically, PR has to be distinguished from conditions which are associated with pagetoid epidermotropic growth and other acral presentations of T-cell lymphomas such as MF palmaris et plantaris (MFPEP), PACTL and Type-D lymphomatoid papulosis (LP-D). Co-expression of CD4 and CD8 in PR is rare but has been described in several literatures. Till date, localized radiation therapy produces the best treatment response.

**Key words:** Woringer-Kolopp disease; Pagetoid reticulosis; Mycosis fungoides

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### INTRODUCTION

Woringer-Kolopp disease is a localized pagetoid reticulosis (PR), which is a very rare variant of mycosis fungoides (MF). It presents as a slow growing lesion which usually occurs at the acral sites. PR is characterized by patches and plaques with an intradermal proliferation of neoplastic T cells. We report a rare co-expression of CD4 and CD8 in PR, presenting with a huge ankle verrucoid plaque, which has the longest clinical course of disease progression reported to our knowledge in the available literature.

### CLINICAL CASE

A 44-year-old Malay lady presented with on-and-off erythematous papular lesions over the leg associated with itchiness since 20 years old but did not seek any treatment. However, 2 years prior to pre-

sentation, her right ankle skin lesion gradually increased in size and eventually turned into a verrucoid plaque. 6 months prior to presentation, the lesion became ulcerated and was associated with foul-smelling pus discharge. It was painless. There was history of skin prick by a sharp sea organism years ago, prior to the initial development of the skin lesion.

On examination, there was a large, verrucous plaque with ulceration and erosion on the right heel, extending to the lower calf (Figure 1).

The extent of the lesion is up to 16cm. There were no cutaneous lesions elsewhere and the remaining systemic and lymph nodes examination also showed no findings. The clinical differential diagnosis by the Dermatology team were chromoblastomycosis and tuberculosis verrucosa cutis.

However, skin biopsy cultures were negative for bacteria, fungi and tuberculosis. TB PCR was also negative. The initial histopathological microscopic examination showed features of mild chronic inflammation with the presence of spongiosis (Figure 2a and 2b).

However, this biopsy was taken from the edge of the lesion. Subsequent skin biopsy performed 2 weeks apart on 23/7/2018 revealed the presence of neoplastic T-cells with cerebriform nuclei, perinuclear halo and nuclear pleomorphism which are confined to the epidermis

with associated acanthosis, hyperkeratosis and parakeratosis (Figure 3,4,5,6).

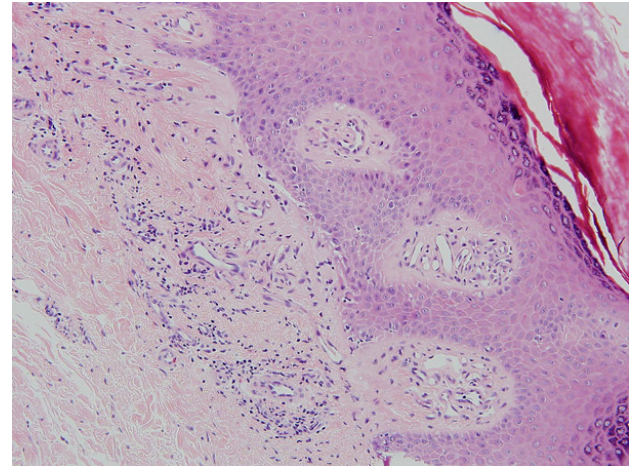


Figure 2a Epidermis displaying acanthosis, hyperkeratosis, hypergranulosis and mild spongiosis with superficial dermal inflammatory infiltrates.



Figure 1 Large, verrucous plaque with ulceration and erosion on the right heel, extending to the lower calf measuring 16cm in extent.

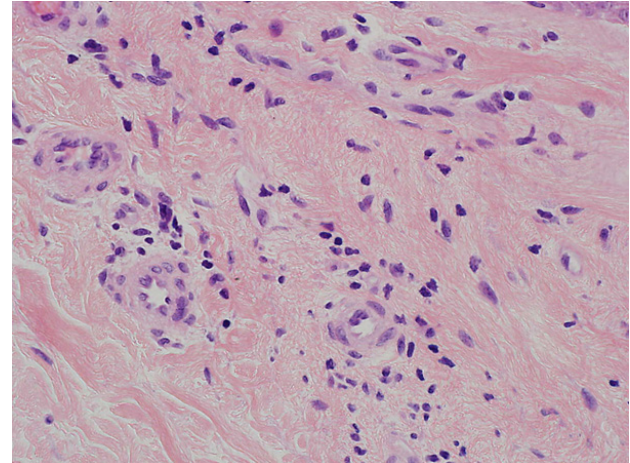


Figure 2b Superficial perivascular infiltration by lymphocytes, histiocytes, mast cells and scattered eosinophils. No atypical lymphoid cells present.

Table 1 Distinguishing features of PR from other conditions which are associated with pagetoid epidermotropic growth and other acral presentations of mycosis fungoides.

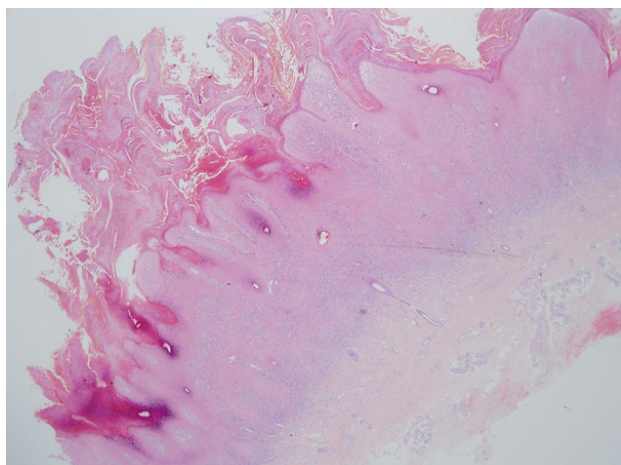
Conditions associated with pagetoid epidermotropic growth pattern	Distinguishing clinical features	Distinguishing histological features	Findings in our case
Superficial spreading melanoma, Paget's disease and pagetoid squamous cell carcinoma in situ [6,8,11].	Paget's disease and pagetoid squamous cell carcinoma in situ may have similar clinical presentation [6]	Distinctive morphologic appearance and immunohistochemistry.	Atypical epidermal infiltrates proven immunophenotypically to be of T-cell origin.
Type-D Lymphomatoid Papulosis [10].	Generalized red papules and nodules (usually less than 1 cm) on the trunk and extremities [10].	Striking epidermotropism of large, CD8+ atypical cells with strong, uniform CD30 expression [10].	Both CD4 and CD8 were expressed. CD30 is negative.
Mycosis fungoides palmaris et plantaris (MFPEP) [3,11,12].	Erythematous, hyperkeratotic, scaly palmar and/or plantar plaques [11].	CD4+ phenotype	The atypical lymphocytes express both CD4 and CD8 and are limited to the epidermis.
		Clinically characterized by thin plaques as opposed to the thickened and often verrucous lesions	Absence of eosinophilic infiltrates.
		Dermal infiltrates may be seen in MFPEP. Eosinophils may be present (Eosinophils are characteristically absent in PR) [11].	
Primary cutaneous aggressive epidermotropic CD8+ T cell lymphoma (PACTL) [11].	Aggressive behaviour with widespread cutaneous lesions	Identical to PR.	The atypical lymphoid cells express both CD4 and CD8 phenotype.
	Poor prognosis [11].	Can be distinguished from some cases of PR with a CD4+ phenotype [11].	Requires long term follow-up to establish diagnosis [11].

These neoplastic cells are positive for LCA, CD3, CD4, CD5 and CD8 with aberrant loss of CD7 expression (Figure 7). They are negative for CD30, CD10, S100, HMB45, Melan A and CD20. The tumour cells display high proliferative index (> 80%) (Figure 8)

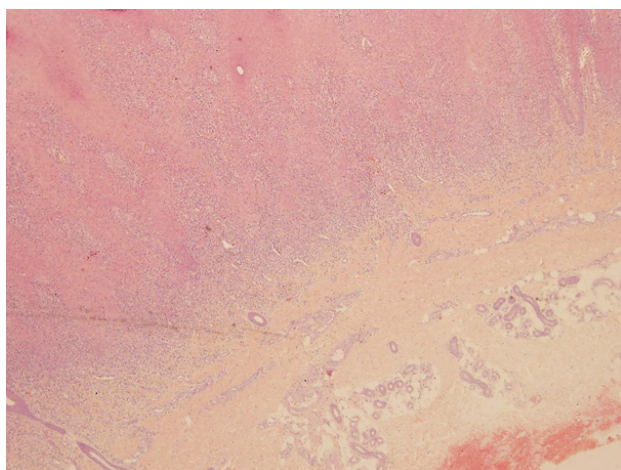
MRI of the right leg shows eccentric, circumferential (covering almost ¾ of the leg) of the posterior part of the distal leg and ankle with suspicious involvement of the Achilles and anterior tibialis tendon. Staging CT scan shows absence of organomegaly, lymphadenopathy and metastasis. No atypical lymphocytes were seen in full blood picture. ESR reading was 35mm/hour and HIV, Hepatitis B and Hepatitis C screening were negative. The local infection was treated with IV cefuroxime and IV amikacin. The lesion was not excised, patient was referred to the oncology team. Subsequently, she received local radiotherapy (24 Gy, 12 fractions) in January 2019. Her condition improved and the verrucous plaque completely disappeared 4 months post radiotherapy. Currently, she is under close follow-up.

## DISCUSSION

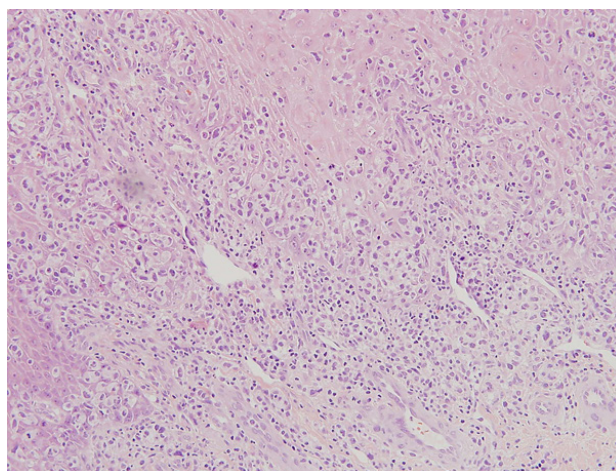
PR was described by Woringer and Kolopp in 1939. It derived its name from the similarity of the epidermotropic lymphocytes to the intraepidermal adenocarcinomatous cells of Paget's disease (PD) of nipple. Its incidence is not well documented in the available literatures. Its disseminated form is known as primary cutaneous aggres-



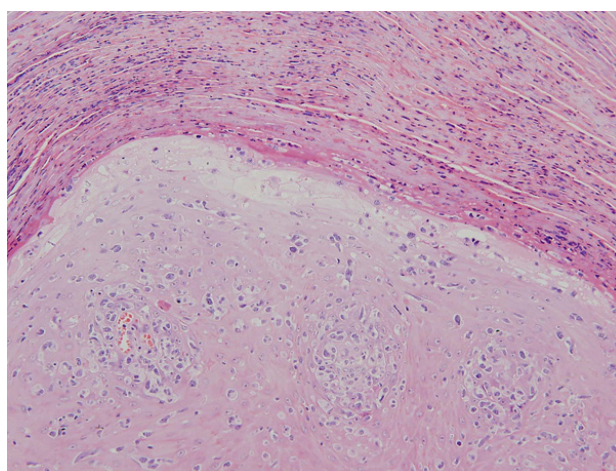
**Figure 3** Low power magnification (2x) displaying papillomatous skin lesion with acanthosis, hyperkeratosis and parakeratosis. Intraepidermal nests of lymphoid cells are noted.



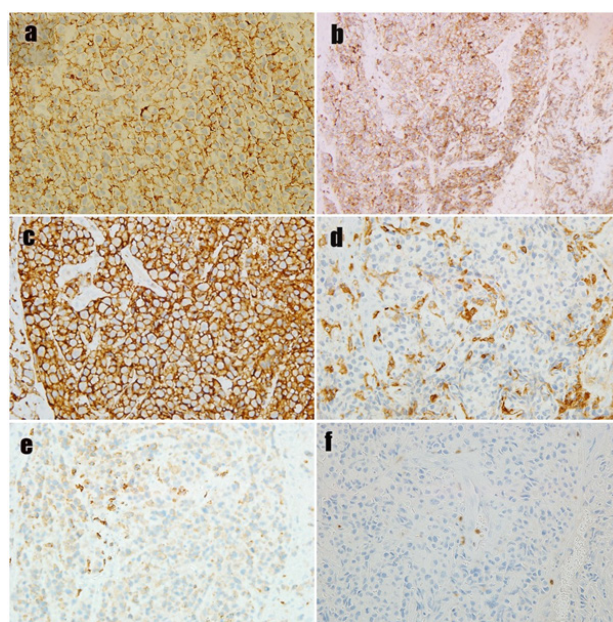
**Figure 4** Low power magnification (4x) of the dermoepidermal junction displaying dense infiltration of lymphocytes and plasma cells at the papillary dermis.



**Figure 5** Low power magnification (20x) of the dermoepidermal junction displaying medium to large-sized neoplastic cells demonstrating nuclear pleomorphism and cerebriform nuclei infiltrating the epidermis.



**Figure 6** Epidermotropism with Pautrier's microabscess formation.



**Figure 7** LCA and T-cell markers expression. (a) LCA (Diffused positivity) (b) CD8 (Diffused positivity) (c) CD5 (Diffused positivity) (d) CD4 (Patchy positivity) (e) CD3 (Focal positivity) (f) Aberrant loss of CD7 expression

sive epidermotropic CD8+ T cell lymphoma (PCACTL); historically known as Ketrion-Goodman disease. As opposed to PCACTL, PR is an indolent disease with excellent prognosis<sup>[4,6]</sup>. It can occur in both children and adults. There is slight male to female predilection with the occurrence ratio of 2:1<sup>[4,8]</sup>. Clinically, PR is characterized by the presence of slow-growing psoriasiform, scaly or crusty patches, plaques or verrucous appearance<sup>[1]</sup>. Due to the nonspecific morphology of a solitary, indolent patch, plaque or verrucous crusted lesion, the clinical differential diagnosis is broad and the lesion can be mistaken for a plaque of Bowen's disease, superficial basal cell carcinoma, discoid eczema, psoriasis or even extramammary Paget's disease, halogenoderma, deep fungal or atypical mycobacterial infection<sup>[8,11]</sup>.

Histopathologically, PR has to be distinguished from other conditions which are associated with pagetoid epidermotropic growth and other acral presentations of mycosis fungoides<sup>[6]</sup>. Biopsy specimens often reveal a dense proliferation of neoplastic T-cells restricted to the epidermis with associated epidermal acanthosis, hyperkeratosis and parakeratosis. The atypical lymphoid cells are moderate to large in size with cerebriform nuclei and abundant clear cytoplasm<sup>[1,10]</sup>.

To date, it is still hard to distinguish PR from other variants of MF such as mycosis fungoides palmaris et plantaris (MFPEP) and PCACTL<sup>[3,11,12]</sup>. MFPEP is invariably of CD4+ phenotype and is clinically characterized by thin plaques as opposed to the thickened and often verrucous lesions associated with presence of prominent epidermotropism in PR<sup>[3,9]</sup>. Dermal infiltrates may be seen in MFPEP in contrast to PR whereby the atypical T-lymphocytes are almost exclusively limited to the epidermis<sup>[11]</sup>. Eosinophils are characteristically absent in PR; which may distinguish PR from other acral presentations of MF<sup>[5,9]</sup>. In our case, the atypical lymphocytes express both CD4 and CD8 phenotype and are limited to the epidermis with absence of eosinophilic infiltrates.

The distinction of PCACTL from PR is mainly clinical. The former shows an aggressive behaviour with widespread cutaneous lesions and renders a poor prognosis. The histomorphological appearances are identical to PR but it can be distinguished from some cases of PR with a CD4+ phenotype<sup>[11]</sup>. Therefore, long term follow-up is required to establish the diagnosis.

Type D lymphomatoid papulosis (LP-D) recaps the striking epidermotropism of PR with the immunophenotype of PCACTL. Presence of strong, uniform CD30 expression put together with the clinical picture will support the diagnosis of LP-D<sup>[10]</sup>.

Although epidermotropism is classically described as a feature of lymphocytes, it can also contain epithelial, melanocytic, neuroendocrine, histiocytic or muscular origin cells<sup>[9]</sup>. Thus, other epidermotropic lesions such as superficial spreading melanoma, Paget's disease and pagetoid squamous cell carcinoma in situ needs to be excluded with careful morphologic assessment and via immunohistochemistry<sup>[10]</sup>. In our case, the atypical epidermal infiltrates have been proven immunophenotypically to be of T-cell origin and they were negative for melanocytic markers.

PR is a proliferative lesion of CD45+ hematopoietic cells of T-cell derivation. Recent studies reported three different phenotypes for the large epidermotropic cells of PR i.e. CD4-positive T-helper phenotype, CD8-positive T-cytotoxic/suppressor phenotype or a CD4/CD8 double-negative phenotype<sup>[1,3]</sup>. The atypical lymphocytes express pan-T-cell antigens such as CD2, CD3 and CD5 with frequent loss or downregulation of CD7<sup>[1]</sup>. Although CD4/CD8 double negative forms have also been described, such cases are probably better regarded as examples of  $\gamma/\delta$  T-cell lymphomas. High levels of expression of CD30 (> 50%) and Ki-67 (50%) may be demonstrated<sup>[2,4,11]</sup>.

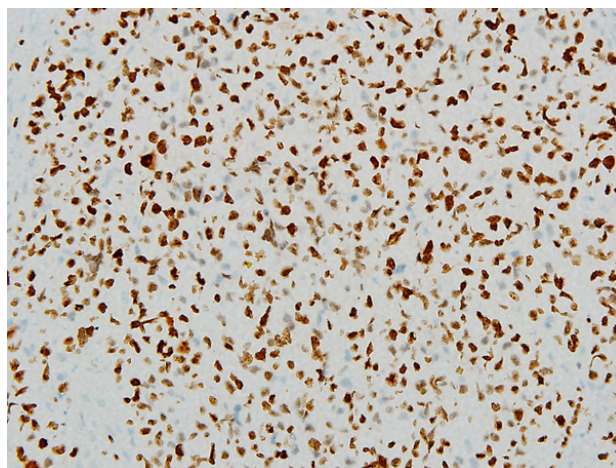


Figure 8 Atypical lymphoid cells displaying high proliferating index.



Figure 9 Lesion has completely resolved 4 weeks post radiotherapy.

The relationship of the proliferative index of the lesional cells to the prognosis is debatable<sup>[3]</sup>. In our case, the epidermotropic atypical lymphocytes have high proliferative index (>80%) and they express both CD4 and CD8 phenotypes with predominant expression of CD8. In addition to the common CD4+, CD8+ or a CD4/CD8 double-negative phenotype, the rarer co-expression of CD4 and CD8 with predominance of either phenotype in PR has also been described in several literatures<sup>[3,4,6]</sup>. However, it is said that these phenotypes have no prognostic significance in PR<sup>[7]</sup>.

Several treatments have been employed in PR cases, such as topical steroids, topical nitrogen mustard, light therapy, interferon alpha-2b, localized and modulated radiation therapy, imiquimod, alitretinoin, fractional laser-assisted photodynamic therapy and excision. However, up to date, localized radiation therapy has shown to produce the best response<sup>[3,8]</sup>. Photodynamic therapy may be an alternative to irradiation in young patients<sup>[3]</sup>.

## CONCLUSION

In summary, our patient presented with PR; a variant of mycosis fungoides that is relatively rare. In our case, both CD4 and CD8 phenotype were co-expressed with predominant expression of CD8. This phenotype is less common but has been reported in several literatures<sup>[3,4,6]</sup>. PR is an indolent disease with good prognosis that can be diagnosed after excluding the other aggressive T-cell lymphomas. Upon diagnosis, long term follow-up is required to exclude PCACTL, which has an aggressive clinical course and poor prognosis<sup>[3,4,6,9]</sup>.

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