

# A case of tegafur/gimeracil/oteracil (TS-1)-induced acral hyperpigmentation: correlation between histopathological features and dermoscopic findings

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Dermoscopy helps detect melanoma on the acral volar skin. A parallel ridge pattern is one of the characteristic dermoscopic findings of melanoma but is also seen in benign lesions, including drug-induced hyperpigmentation. Histological examination is therefore necessary for definitive diagnosis. A 74-year-old Japanese man was referred to our department with irregular-shaped brown macules on his palms and soles. The pigmented lesions had a parallel ridge pattern on dermoscopic examination. The largest lesion was resected at the patient's insistence and considering the possibility of melanoma. Histopathological examination revealed increased melanin granules in basal keratinocytes and many melanophages in the superficial dermis, especially underlying the crista profunda intermedia, agreeing with the dermoscopic findings. The patient had been receiving tegafur-gimeracil-oteracil (TS-1) for advanced gastric cancer. The pigmented lesions gradually regressed after cessation of TS-1, consistent with TS-1-induced hyperpigmentation. Further studies are needed to elucidate the pathogenesis, including analyses of the relationship between acrosyringal endothelin-1 expression and the presence of volar melanocytes in relation to potential drug metabolism.

**Keywords:** hyperpigmentation, tegafur-gimeracil-oteracil, parallel ridge pattern, melanoma

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## INTRODUCTION

Although a parallel-ridge pattern is a well-known dermoscopic finding in acral melanoma, it has also been demonstrated in certain benign plantar lesions, such as congenital or acquired nevi, subcorneal hemorrhage, dye-related pigmentation, and drug-induced hyperpigmentation <sup>1</sup>. Lentiginosis is a well-known adverse effect of tegafur/gimeracil/oteracil

(TS-1) administration <sup>2</sup>. However, few studies have defined its histopathological features in relation to the dermoscopic findings. These findings are reported in this case report.

## CASE REPORT

A 74-year-old Japanese man visited our department complaining of irregular-shaped brown macules on

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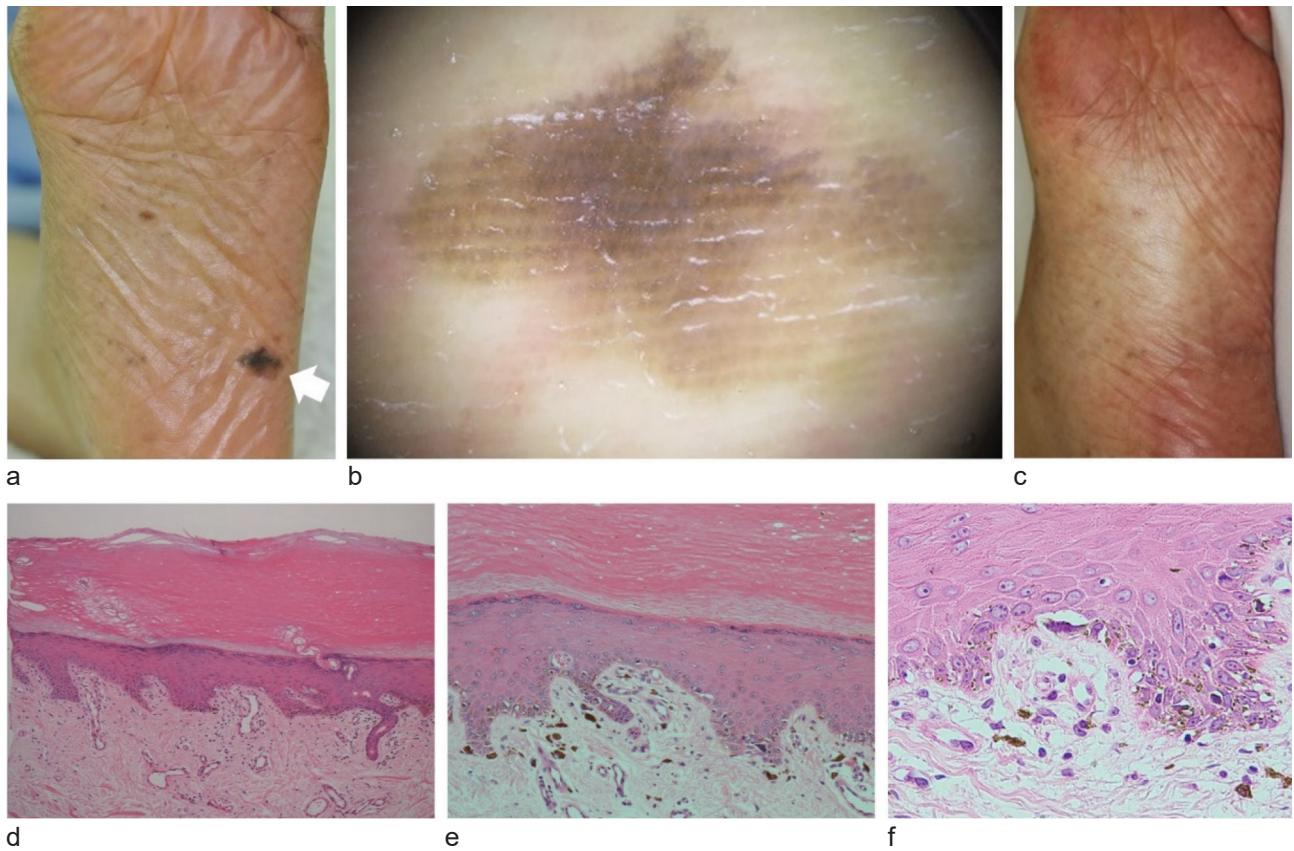
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his palms and soles that he had noticed a month before (Figure 1A). He had been suffering from an advanced stage of gastric cancer, receiving TS-1 (120 mg/daily) chemotherapy for four months. Intestinal tract polyposis was not detected by colonic endoscope examination, thus ruling out Peutz-Jeghers syndrome. The pigmented lesions had a parallel ridge pattern on dermoscopic examination (Figure 1B). There were a total of 12 lesions on the palms and the soles. The largest, measuring  $1.8 \times 1$  cm (Figure 1A, arrow), was resected at the patient's insistence, with a narrow margin (1 mm). Histopathological examination showed increased melanin granules in the basal keratinocytes and many melanophages in the superficial dermis, especially underlying the crista profunda intermedia, which contained sweat ducts (Figure 1C). Some melanocytes had large, bizarre, atypical nuclei, which a dermatopathologist suggested indicated a potential diagnosis of melanoma in situ (Figure 1D, E). Immunohistochemical analysis for cleaved caspase-3, an apoptosis-associated protein,

was negative in the melanocytes. After cessation of TS-1 because of treatment regimen alteration, the residual pigmented lesions gradually regressed, and there was no recurrence in the resected area (Figure 1F). The patient died from primary disease progression shortly after that.

### DISCUSSION

The parallel ridge pattern has 99% specificity in the detection of both melanoma in situ and advanced melanoma on the acral volar skin—a significance that is a recent advance in dermoscopy<sup>3</sup>. However, it is possible for this characteristic pattern also to be seen in some pigmented lesions, such as congenital or acquired nevi, subcorneal hemorrhage, dye-related pigmentation, acral pigmented macules associated with Peutz-Jeghers syndrome, and anti-cancer drug-induced hyperpigmentation<sup>3</sup>. One of the most common causes of such pigmented lesions is the widely-used anti-cancer agent TS-1, approved for treating gastric, head and neck, colorectal, non-small-cell lung, breast,



**Figure 1.** Brown macules on the left foot (a); the largest lesion (arrow) was resected. Parallel ridge pattern on dermoscopic examination (b). Increased melanin in basal keratinocytes and melanophages (c). Proliferation of melanocytes along the dermo-epidermal junction as solitary units (d). Melanocytes with large bizarre atypical nuclei (e). Lesions after discontinuation of TS-1, with scarring (f).

pancreatic, and biliary tract cancers<sup>2</sup>. The pathogenic mechanism of TS-1-induced acral hyperpigmentation is not fully understood, but the involvement of drug metabolism has been suggested<sup>1</sup>.

Here, we observed melanin deposition in the melanocytes and surrounding basal keratinocytes, marked melanin incontinence, and the presence of melanophages, especially under the crista profunda intermedia. The relationship between acrosyringeal endothelin-1 expression and the presence of melanocytes at volar sites may explain these histopathological features and the dermoscopic parallel ridge pattern<sup>4</sup>. In addition to these findings, some of the melanocytes were found to have atypical large nuclei, as pointed out in a previous study<sup>5</sup>. To study the involvement of cell degeneration and apoptosis in this pathogenesis, we performed an immunohistochemical analysis for cleaved caspase-3, which returned negative. Further biological studies are needed to elucidate how TS-1 affects the metabolic regulation of cell proliferation and the differentiation of melanocytes.

## CONCLUSION

A parallel ridge pattern is one of the characteristic dermoscopic findings of melanoma on the volar aspects of the hand and foot. However, it is not necessarily specific to melanoma, and histological examination is needed for definitive diagnosis. This case study indicated the relationship between the dermoscopic and histological findings in TS-1-induced acral hyperpigmentation. Further studies are needed to elucidate the pathogenesis of this condition.

## Authors contributions

YK was major contributor, acquired and analyzed patient data, wrote and submit the manuscript. KST contributed to acquisition, and interpretation of data for the work. MK performed histological examination of the skin. TN and MF provided his expertise and supervised the manuscript. All authors read and approved the final manuscript.

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**Conflict of Interest:** None declared.

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