Received: 15 August 2023 | Revised: 20 September 2023 | Accepted: 5 October 2023

DOI: 10.1002/jvc2.295

JEADV CLINICAL PRACTICE
OPEN ACCESS JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

CASE REPORT

Histopathologic features of selumetinib-induced paronychia in a child with neurofibromatosis type 1

P. Borgia[1,2] | **J. Ferro**[3] | **G. Piccolo**[1,4] | **P. Striano**[1,2] | **V. G. Vellone**[3,5] | **G. Viglizzo**[6] | **M. C. Diana**[2]

[1]Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy

[2]Pediatric Neurology and Muscular Diseases Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy

[3]Pathology Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy

[4]Neuro-Oncology Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy

[5]Department of Surgical Sciences and Integrated Diagnostic (DISC), University of Genoa, Genoa, Italy

[6]Dermatology and Angioma Center, IRCCS Istituto Giannina Gaslini, Genoa, Italy

Correspondence
G. Viglizzo, Dermatology and Angioma Center, IRCCS Istituto Giannina Gaslini, Via Gerolamo Gaslini 5, Genoa 16147, Italy.
Email: gianmariaviglizzo@gaslini.org

Funding information
ALNEURORF PROV124/23 Research Program

Abstract

We report a 4-year-old girl developing therapy refractory paronychia induced by selumetinib, an oral selective inhibitor of mitogen-activated protein kinase 1/2 prescribed for a large submandibular plexiform neurofibroma. Although this cutaneous reaction is well-known and more prevalent in children than in adults, no histopathological characterisations of nail unit toxicity in children on selumetinib have been reported so far. We show histopathological studies on patient-derived periungual inflamed skin to investigate the cutaneous impact of selumetinib therapy. Our findings are consistent with those of epidermal growth factor receptor inhibitors and support the role of a non-specific immune activation rather than opportunistic infection in the underlying mechanism of the disease. Partial bilateral matricectomies with electrocautery were resolutive, and the child restarted selumetinib with no recurrence of paronychia during a follow-up period of 3 months after nail surgery.

KEYWORDS
drug response, MEK inhibitors, nail toxicity, oncology, paediatric dermatology, paronychia

P. Borgia and J. Ferro contributed equally to this study.

INTRODUCTION

Selumetinib is an oral selective inhibitor of mitogen-activated protein kinase 1/2, recently approved for the treatment of inoperable plexiform neurofibromas in children.[1] A common cutaneous reaction to selumetinib is the development of paronychia, possibly evolving into onychocryptosis with onset time ranging from weeks to several months after the start of treatment.[1] Chronic paronychia is challenging to treat and may lead to early therapy discontinuation.[2] Although this cutaneous reaction is well-known, no histopathological characterisations of nail unit toxicity in children have been reported.

CASE REPORT

We report a 4-year-old female with neurofibromatosis type 1 (NF1), carrying a heterozygous *NF1* gene mutation (c.3721C>T; p.R1241X), referred for a severely painful left submandibular plexiform neurofibroma. Since a surgical approach was not practicable, oral selumetinib at a dose of 20 mg twice daily was introduced. Within 12 months of starting treatment with selumetinib, the child exhibited a drastic tumour shrinkage, but she concomitantly reported painful periungual folds of the bilateral halluces. Examination revealed oedema and redness of the bilateral nailfolds. As she denied any trauma, infection or other drug assumption, we suspected selumetinib-induced paronychia. Since combination topical therapy with antibiotics and steroids (fusidic acid and betamethasone 0.1%) failed, topical tacrolimus 0.03% twice daily and oral treatment with azithromycin at 10 mg/kg three times per week were attempted.[3] These treatments were ineffective, and selumetinib was therefore discontinued. Three months later, a follow-up MRI documented tumour regrowth, so she restarted selumetinib at a lower dose (10 mg twice daily). The paronychia recurred with worsened clinical features (Figure 1). Therefore, she underwent bilateral partial matricectomies with electrocautery and biopsy over the inflamed periungual site. Histopathological analysis showed a marked chronic infiltrate of mixed inflammatory cells, prominent thin-walled vessels and diffuse oedema (Figure 2). PAS and Grocott histochemical stainings for fungal hyphae and spores were negative. The child restarted selumetinib (20 mg twice daily) with no recurrence of paronychia during a follow-up period of 3 months after nail surgery.

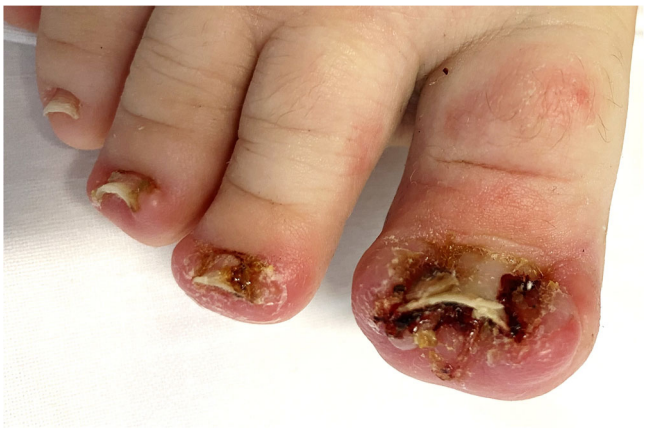

FIGURE 1 Clinical image of selumetinib-induced paronychia before nail surgery. Painful erythematous periungual oedema with sterile pus, subungual haemorrhage, brittle nails and onychocryptosis.

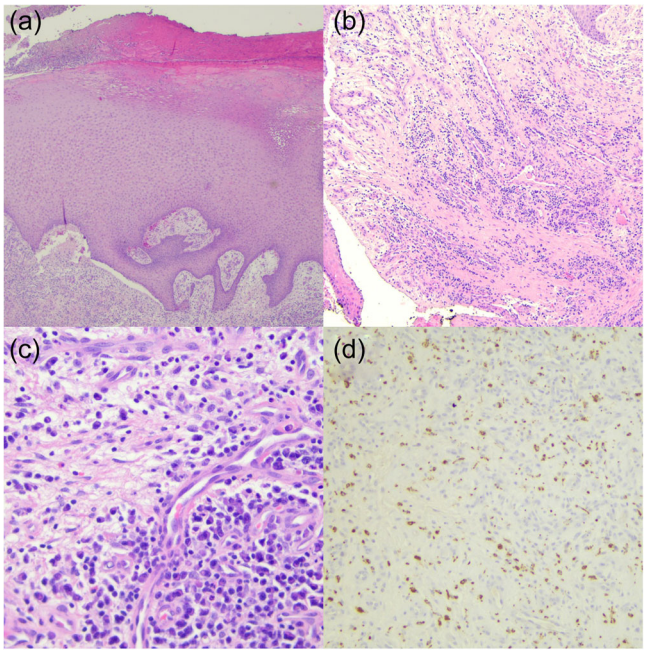

FIGURE 2 Histopathologic image of chronic paronychia. (a) Shave biopsy specimen from inflamed periungual tissue showing marked acanthosis, parakeratosis and spongiosis of the epidermis (haematoxylin–eosin; original magnification ×2). (b) There is a chronic inflammatory infiltrate arranged in a perivascular and diffuse pattern and associated with numerous newly formed thin-walled vessels with reactive endothelium (haematoxylin–eosin; original magnification ×10). (c) The inflammatory infiltrate is predominantly composed of plasma cells, lymphocytes, neutrophils, and eosinophils (haematoxylin–eosin; original magnification ×40). (d) On immunohistochemical investigation for CD68, several histiocytes were also observed in the absence of granuloma formation (original magnification ×10).

DISCUSSION

Paronychia is a well-known side effect induced by various chemotherapeutic agents, including but not limited to selumetinib.[3] Although selumetinib treatment reports the highest incidence rates of paronychia, particularly in children compared to adults,[4] histopathologic features of this condition have not been previously described in detail. Literature data suggest that selumetinib shares similar clinical and histopathologic reaction patterns with those of the epidermal growth factor receptor inhibitors (EGFRIs), as they may target different levels of the same molecular pathway, consisting of Raf/MEK/Erk mitogen-activated protein kinase (MAPK) cascade.[5] Specifically, EGFR inhibition is known to lead to premature differentiation and apoptosis of keratinocytes, driving the release of chemokines with consequent recruitment of inflammatory cells, vascular dilation and increased permeability.[6]

In this report, histologic analysis revealed an abnormal epidermis with parakeratosis, prominent vessels in the dermis and a chronic inflammatory infiltrate with both diffuse and perivascular patterns within an oedematous stroma. These findings are consistent with those of EGFRIs,[6,7] supporting the role of a non-specific immune activation rather than opportunistic infection in the underlying mechanism of the disease. Nevertheless, based on the limited existing literature, the histopathological features delineated in this study lack specificity, as similar changes in the epidermis and chronic inflammation in the subepithelial connective tissue were observed in other types of chronic paronychia, including juvenile ingrown toenails and chronic paronychia caused by mechanical or chemical factors.[8,9] In addition, comparable features can be found in cases of chronic paronychia induced by other systemic medications, such as taxanes,[10] CD20 antagonists,[11] vascular endothelial growth factor inhibitors[12] and retinoids.[13] While the underlying pathomechanisms may differ across the several forms of chronic paronychia, they ultimately lead to varying degrees of inflammatory activation, depending on the clinical stages of the disease.

Furthermore, the child experienced clinical improvement upon discontinuing selumetinib, suggesting the absence of underlying infectious processes. In addition, the patient was resistant to conventional treatment, and the use of doxycycline, considered effective in refractory paronychia, was not allowed due to age prescription limitations. Thus, based on a previous report,[14] we attempted the use of azithromycin at low doses and long-term administration, taking advantage of its anti-inflammatory properties, without achieving satisfactory effects.

An important aspect of the management of children treated with MEK inhibitors lies in preventive measures to minimise periungual trauma and inflammation.[14,15] These include wearing comfortable shoes, avoiding aggressive manicuring, onychophagia and onychotillomania, and using nail lacquer to prevent nail fragmentation. Topical corticosteroids associated with an antiseptic should be administered as soon as a periungual erythema appears.[15]

In conclusion, selumetinib-induced paronychia may exhibit a histological pattern similar to EGFRIs and other types of chronic paronychia, underscoring the significance of the patient's medical history. Clinical trials should develop strategies for minimising the risk of selumetinib-associated paronychia.

AUTHOR CONTRIBUTIONS

P. Borgia, P. Striano, G. Viglizzo and M. C. Diana conceptualised the manuscript. P. Borgia, J. Ferro and G. Piccolo drafted the manuscript. M. C. Diana, G. Viglizzo, P. Borgia and G. Piccolo were involved in the clinical care of the patient. J. Ferro and V. G. Vellone conducted the histopathological studies. P. Striano, G. Viglizzo and M. C. Diana final acquisition, interpretation of clinical data and drafting and reviewing the manuscript. All authors have critically revised the manuscript and approved the final one as submitted.

ACKNOWLEDGEMENTS

This study was supported by ALNEURORF PROV123/23 Research Program “Ricerca Corrente Reti” - RCR-2022-23682290 - Rete RIN Application of Artificial Intelligence Methods to TELENEUROREHABILITATION.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

ETHICS STATEMENT

The parents/guardians of minor patients have given written informed consent for their child's participation in the study, as well as for the use of their child's de-identified, anonymized, aggregated data and case details (including photographs) for publication.

ORCID

P. Borgia https://orcid.org/0000-0002-3520-915X

REFERENCES

1. Gross AM, Wolters PL, Dombi E, Baldwin A, Whitcomb P, Fisher MJ, et al. Selumetinib in children with inoperable plexiform neurofibromas. N Engl J Med. 2020;382(15):1430–42.
2. Sharawat IK, Panda PK, Sihag RK, Panda P, Dawman L. Efficacy and safety profile of selumetinib in symptomatic inoperable plexiform neurofibromas. J Neurosurg Sci. 2022; 66(6):501–10.
3. Curry JL, Torres-Cabala CA, Kim KB, Tetzlaff MT, Duvic M, Tsai KY, et al. Dermatologic toxicities to targeted cancer therapy: shared clinical and histologic adverse skin reactions. Int J Dermatol. 2014;53(3):376–84.
4. Boull CL, Gardeen S, Abdali T, Li E, Potts J, Rubin N, et al. Cutaneous reactions in children treated with MEK inhibitors, BRAF inhibitors, or combination therapy: a multicenter study. J Am Acad Dermatol. 2021;84(6):1554–61.
5. Balagula Y, Barth Huston K, Busam KJ, Lacouture ME, Chapman PB, Myskowski PL. Dermatologic side effects associated with the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886). Invest New Drugs. 2011;29(5):1114–21.
6. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. Nat Rev Cancer. 2006;6(10):803–12.
7. Nakano J, Nakamura M. Paronychia induced by gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor. J Dermatol. 2003;30(3):261–2.
8. Fernandez-Flores A, Martínez-Nova A, Salgado-Fernandez S. Ingrown toenail: histopathologic and immunohistochemical study. Am J Dermatopathol. 2009;31(5):439–45.
9. Rocha BP, Verardino G, Leverone A, D'Almeida LFV, Azulay V, Haneke E, et al. Histopathological analysis of chronic paronychia. Int J Dermatol. 2023;62(4):514–7.
10. Sibaud V, Lebœuf NR, Roche H, Belum VR, Gladieff L, Deslandres M, et al. Dermatological adverse events with taxane chemotherapy. Eur J Dermatol. 2016;26(5):427–43. https://doi.org/10.1684/ejd.2016.2833
11. Wollina U. Multiple eruptive periungual pyogenic granulomas during anti-CD20 monoclonal antibody therapy for rheumatoid arthritis. J Dermatol Case Rep. 2010;4(3):44–6.
12. Wollina U. Systemic drug-induced chronic paronychia and periungual pyogenic granuloma. Indian Dermatol Online J. 2018;9(5):293–8.
13. Baran R. Etretinate and the nails (study of 130 cases) possible mechanisms of some side-effects. Clin Exp Dermatol. 1986;11: 148–52.
14. Borgia P, Piccolo G, Diana MC, Viglizzo G. Chemotherapy-associated paronychia: do not forget the children. J Am Acad Dermatol. 2023;88(1):e59.
15. Wetzel ML, Rubin AI, Hanania H, Patel AB. Treatment recommendations for nail unit toxicities secondary to targeted cancer therapy based on collective experience and evidence-based literature review. J Am Acad Dermatol. 2022;87(1): 180–3.

How to cite this article: Borgia P, Ferro J, Piccolo G, Striano P, Vellone VG, Viglizzo G, et al. Histopathologic features of selumetinib-induced paronychia in a child with neurofibromatosis type 1. JEADV Clin Pract. 2023;1–4. https://doi.org/10.1002/jvc2.295