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Nail Toxicities Associated With Anticancer Therapies in Children

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ABSTRACT

Nail toxicities are a frequent yet often underrecognized component of dermatologic adverse events in children receiving anticancer therapies. Both conventional cytotoxic chemotherapy and newer targeted agents can affect the nail matrix, nail bed and periungual tissues, producing a broad spectrum of clinical manifestations that range from asymptomatic pigmentary alterations to painful inflammatory conditions with functional impairment. Conventional chemotherapy most commonly induces manifestations such as melanonychia, leukonychia, Beau's lines, onychomadesis, onycholysis and nail fragility because of transient or sustained damage to rapidly proliferating nail matrix cells. These alterations typically involve multiple nails. Although generally self-limited, their delayed onset and resolution, due to intrinsic nail growth kinetics, may complicate temporal correlation with drug exposure and may still affect patients' quality of life. In contrast, targeted therapies, particularly MEK inhibitors, are predominantly associated with inflammatory periungual toxicities such as chronic paronychia and periungual pyogenic granulomas, which may be painful, prone to bleeding, and functionally limiting the quality of life. Emerging agents, including BRAF inhibitors, multi-tyrosine kinase inhibitors, mTOR inhibitors and ALK inhibitors, share partially overlapping nail toxicity profiles, though usually with lower frequency or severity compared with MEK inhibitors. Early recognition of characteristic nail patterns is essential to prevent unnecessary investigations, misdiagnosis, and avoidable interruption of oncologic therapy. Management is largely conservative and includes protective measures, topical therapies, systemic anti-inflammatory agents when indicated, and procedural interventions for refractory periungual lesions. A multidisciplinary approach involving paediatric oncologists and dermatologists is crucial to optimize symptom control, maintain treatment adherence and preserve quality of life in paediatric patients.

1 | Introduction

Paediatric oncology patients frequently develop dermatologic adverse events related to systemic anticancer therapies, and these toxicities may involve not only the skin and mucosae, but also adnexal structures such as hair and nails [1, 2]. Although cutaneous toxicities have been extensively characterized in adult oncology [3–5], paediatric-specific data remain limited, and most available evidence derives from small prospective cohorts or systematic reviews focusing on selected therapeutic classes [1, 2, 6, 7]. In a prospective study of children undergoing oncological drugs, nearly all patients developed at least one dermatologic manifestation during treatment, with nail changes reported in 20% of patients [1].

It should be noted that children's nails differ from adult nails in several anatomical and biological aspects. At birth, nails are already fully formed but are thinner and softer than in adults, and their size is related to gestational age and birth weight. Nail growth progressively increases with age and reaches a rate similar to that of adults around 10–14 years of age. In addition, some features are physiologic and age-specific in newborns,

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Summary

- Cancer in children is rare, but every year many children around the world are treated for leukaemia, brain tumours, and other types of cancer. Modern treatments have greatly improved survival. However, these treatments can cause different side effects, such as in the nails.
- The goal of this review was to explain which nail problems can happen during cancer treatment in children, why they occur, and how they can be treated safely.
- We reviewed scientific literature about children receiving chemotherapy (traditional anticancer drugs) and newer targeted therapies (drugs that act on specific cancer pathways). We focused on nail changes in colour, structure, nail shedding and painful swelling around the nails.
- We found that traditional chemotherapy mainly affects the part of the nail apparatus that produces new nail (the matrix), leading to colour changes, surface abnormalities, fragility or temporary nail shedding. These changes usually affect several nails at the same time and improve slowly as the nail grows. Newer targeted drugs, especially MEK inhibitors, more often cause painful inflammation around the nails and small bleeding growths called pyogenic granulomas. These can interfere with walking, sports or daily activities.
- Most nail changes are not severe and do not require stopping cancer treatment. Early recognition, simple protective measures, creams and sometimes minor surgical procedures can control symptoms. Close collaboration between paediatric oncologists and dermatologists helps children continue life-saving therapy while maintaining comfort and quality of life.

including mild koilonychia, especially of the toenails, and transient light-brown pigmentation of the proximal nail fold. These age-related characteristics may influence both the clinical appearance and the interpretation of nail changes in paediatric patients [8].

Nail toxicities represent a frequent yet still underrecognized adverse effect of cancer therapies, encompassing a broad spectrum of clinical presentations that range from mild 'cosmetic' alterations to painful and functionally limiting conditions [9–11]. Both conventional cytotoxic chemotherapies and newer targeted agents have been associated with nail alterations, affecting the nail plate, nail bed and periungual tissues through distinct but sometimes overlapping pathogenic mechanisms [2, 9, 10, 12]. Conventional chemotherapeutic agents have classically been linked to melanonychia, leukonychia, onychomadesis, Beau's lines and onychorrhexis, reflecting transient or sustained impairment of nail matrix proliferation and keratinization, while onycholysis is due to inflammation of the nail bed inducing a detachment from the nail plate [9, 10]. In contrast, targeted therapies, particularly MEK inhibitors, are frequently associated with inflammatory periungual manifestations such as paronychia and pyogenic granuloma-like lesions, which may be painful and bleeding [9, 10, 13, 14].

The type and severity of nail alterations are influenced by the specific drug class, dosage, cumulative exposure, treatment duration and use of combination regimens [9, 10]. Although many nail changes are reversible after treatment discontinuation, their onset and resolution are delayed due to the intrinsic kinetics of nail growth, which averages approximately 3 mm per month for fingernails and 1 mm per month for toenails, thereby complicating temporal correlation with drug exposure [10]. Nail toxicities should not be regarded as merely cosmetic adverse events, as they can cause pain, functional impairment, and substantial psychosocial distress, potentially leading to dose reduction, treatment interruption or even cessation of oncologic therapy [2, 9, 10].

In paediatric patients, timely recognition and management of dermatologic adverse events are particularly critical because these toxicities may compromise adherence to treatment protocols that are often intensive and prolonged [2]. In addition, paediatric malignancies differ biologically from adult cancers in terms of tumour origin, mutational burden, and immune microenvironment, and these differences may influence both the incidence and clinical expression of treatment-related cutaneous and nail toxicities [2].

The Common Terminology Criteria for Adverse Events (CTCAE) is widely used in oncology to grade treatment-related toxicities, including nail changes; however, this classification may not fully capture the heterogeneity, severity spectrum or quality-of-life impact of nail alterations [9, 10, 15]. Indeed, CTCAE was primarily developed for use in clinical trials and was not specifically designed to comprehensively evaluate nail disorders in routine practice, potentially leading to underestimation of their clinical burden [9, 10, 15].

Given the increasing integration of targeted therapies and immunotherapies into paediatric oncology protocols, alongside conventional chemotherapy, the spectrum of nail toxicities is expanding, and dermatologists and oncologists must be aware of both classic and emerging patterns of nail involvement [2, 9]. Despite growing awareness in adult oncology, paediatric-focused data remain scarce, highlighting the need for comprehensive synthesis of available evidence to better characterize nail toxicities in children receiving anticancer treatments [1, 2, 16]. For these reasons, this narrative review aims to summarize the current literature on nail toxicities induced by oncologic therapies in paediatric patients, with the goal of improving recognition, classification and management of these clinically relevant adverse events [1, 2, 9, 16].

2 | Chemotherapy

Conventional cytotoxic chemotherapy, still fundamental in paediatric oncology, frequently causes dermatological adverse events because it targets proliferating tissues, such as the nail matrix, rapidly [1, 17, 18]. As a result, children receiving multiagent protocols for leukaemias, lymphomas and solid tumours often develop characteristic nail alterations involving multiple digits simultaneously [10, 16].

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The spectrum includes pigmentary alterations, transverse growth arrest depression, fragility and nail detachment, forming a recognizable pattern of chemotherapy-related nail toxicity [9, 10]. Although generally benign and self-limited, these alterations may cause discomfort and concern in children and caregivers, making their recognition important to avoid unnecessary investigations or treatment interruption [1, 12].

2.1 | Melanonychia

Melanonychia represents one of the most frequent nail alterations associated with systemic anticancer therapy and, although well described in adults, it is increasingly recognized in paediatric oncology patients undergoing conventional chemotherapy [1, 9, 10].

Clinically, melanonychia appears as brownish pigmentation of the nail plate presenting as longitudinal bands (Figure 1), transverse bands, or diffuse discolouration, often involving multiple nails symmetrically, a pattern highly suggestive of a systemic drug-induced aetiology [10, 17, 19, 20].

Among cytotoxic agents, cyclophosphamide and anthracyclines such as doxorubicin, widely used in paediatric leukaemia and solid tumour protocols, are the drugs most commonly associated with melanonychia, producing diffuse or banded nail pigmentation [17, 21]. Hydroxyurea, administered in paediatric haematologic malignancies, may also induce extensive melanonychia, sometimes involving all nails [22]. Other regimens, including vincristine and methotrexate, can produce transverse melanonychia corresponding to treatment cycles, due to repeated toxic injury to the matrix [23, 24].

The pathogenesis is primarily related to melanocytic activation rather than melanocytic proliferation, meaning the number of melanocytes remains stable while melanin production increases [9, 19, 20]. Cytotoxic injuries in the nail matrix induce the release of inflammatory mediators and growth factors that stimulate normally quiescent melanocytes to synthesize melanin and transfer it to surrounding keratinocytes of the nail plate [10, 12]. This mechanism is analogous to post-inflammatory hyperpigmentation and explains why several nails may be involved simultaneously without structural alterations of the nail plate [4, 9].

FIGURE 1 | Longitudinal melanonychia affecting multiple fingernails, secondary to treatment for paediatric leukaemia.

In cyclical chemotherapy regimens, transverse melanonychia may rarely occur as a result of intermittent melanocyte activation corresponding to repeated treatment cycles, although chemotherapy-induced melanonychia more commonly presents as longitudinal bands or diffuse nail pigmentation [10, 23].

Despite its alarming appearance, chemotherapy-related melanonychia is typically asymptomatic and rarely requires modification of oncologic therapy [1, 17]. Multiple nail involvement, temporal association with chemotherapy, and absence of periungual involvement help distinguish it from melanocytic neoplasms in paediatric patients [19, 20].

Regression occurs after drug withdrawal and depends on nail growth rate, usually requiring several months for fingernails and longer for toenails until the pigmented plate grows out completely [9, 10]. Recognizing chemotherapy-induced melanonychia as a benign and self-limited toxicity is essential to prevent misdiagnosis and avoid unnecessary interruption of life-saving treatment in children [1, 9].

2.2 | Leukonychia

Leukonychia is defined as a white discolouration of the nail and represents one of the most characteristic nail manifestations observed during systemic anticancer therapy, including in paediatric oncology patients (Figure 2) [10, 16]. Leukonychia is traditionally divided into true leukonychia, apparent leukonychia, and pseudoleukonychia according to the anatomic site of alteration within the nail unit [25]. True leukonychia originates in the nail matrix and produces opaque white discolouration that does not fade with pressure and migrates distally with nail growth because it is incorporated into the nail plate keratin [25]. In contrast, apparent leukonychia derives from nail bed vascular alterations and therefore blanches with digital pressure and remains stationary during nail growth, since the nail plate is structurally normal [25]. Pseudoleukonychia instead results from superficial nail plate changes such as surface infection or external alteration and disappears with scraping because the pathology does not involve matrix or nail bed, and generally is not related to oncological treatment [19, 25].

In oncologic patients the most frequent chemotherapy-related form is transverse leukonychia, which may correspond either to Mees' lines (true leukonychia) or Muehrcke's lines (apparent

FIGURE 2 | Apparent leukonychia in a child.

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FIGURE 3 | Muehrcke's lines in a paediatric patient, presenting as symmetric paired transverse white bands involving multiple fingernails, associated with repeated chemotherapy cycles.

FIGURE 4 | Onycholysis affecting multiple fingernails, secondary to cytarabine.

leukonychia), both appearing as parallel white bands across multiple nails [26, 27]. Muehrcke's lines appear to be among the most frequently reported chemotherapy-related nail alterations, although direct comparative data with adult patients are limited [16].

Muehrcke's lines (Figure 3) are particularly common in children receiving chemotherapy and appear as paired narrow transverse white bands parallel to the lunula that fade with pressure and do not move with nail growth [10, 24]. These bands often involve several nails symmetrically and may become more evident during repeated treatment cycles [16, 17].

Several cytotoxic drugs used in paediatric oncology have been associated with leukonychia, including cyclophosphamide, doxorubicin, vincristine and antimetabolites administered in leukaemia protocols [10, 27]. Anthracyclines such as daunorubicin have also been reported to induce transverse leukonychia corresponding to chemotherapy cycles [28].

The pathogenesis differs depending on the leukonychia subtype. Mees' lines result from temporary impairment of matrix keratinization caused by cytotoxic damage to proliferating keratinocytes, leading to parakeratotic cells that scatter light and appear white [10, 25]. Because the abnormal keratin becomes incorporated into the growing plate, the white bands migrate distally over time, allowing retrospective dating of the toxic insult [12, 26]. In contrast, Muehrcke's lines are caused by vascular congestion and altered perfusion of the nail bed rather than structural plate damage, which explains blanching on pressure and absence of migration [10, 25].

Leukonychia is usually asymptomatic and rarely requires modification of oncologic therapy in children [16, 17].

2.3 | Onycholysis

Onycholysis is defined as the distal detachment of the nail plate from the nail bed and appears clinically as a white-yellow area caused by air under the detached plate (Figure 4) [19, 29]. Although less frequent than pigmentary alterations, onycholysis represents a well-recognized nail adverse event during systemic chemotherapy and may occur in paediatric oncology patients receiving cytotoxic regimens [10, 17]. Antineoplastic agents can damage rapidly dividing cells of the nail apparatus, and toxicity affecting the nail bed is specifically associated with the development of onycholysis [4, 12]. Multiple nails are usually involved symmetrically [10, 19].

In children, drugs such as cytarabine and multiagent leukaemia protocols have been reported to induce onycholysis [17]. Clinically, detachment may occur alone or together with subungual haemorrhage or discolouration and can involve multiple nails [10, 19].

Taxanes, although less frequently used in paediatric oncology compared with adult solid tumours, are administered in selected childhood malignancies such as sarcomas, central nervous system tumours and refractory or relapsed solid cancers, and they are among the chemotherapeutic agents most strongly associated with nail toxicity [12, 17]. In this context, onycholysis represents one of the characteristic painful nail adverse events, often accompanied by subungual haemorrhage, nail bed tenderness and occasionally periungual inflammation [10, 12].

Because the detached nail plate exposes the nail bed, secondary bacterial or fungal colonization and pain are relatively common and may significantly affect daily activities in children [12]. Microbiologic evaluation is recommended when pain or discharge is present [12].

The condition is usually reversible, but complete re-adhesion depends on nail growth and may require several months after drug withdrawal [10, 12].

2.4 | Onychomadesis and Beau's Lines

Beau's lines are transverse depressions of the nail plate caused by temporary arrest of nail matrix proliferation, whereas onychomadesis represents a more severe form of the same process leading to proximal separation and shedding of the nail plate [10, 19]. These alterations reflect acute damage to rapidly dividing matrix keratinocytes and therefore occur frequently during exposure to cytotoxic chemotherapeutic agents [4, 12, 18]. The depth of the depression correlates with the extent of damage to the nail matrix, and the width is proportional to the duration of the insult [18].

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FIGURE 5 | Beau's lines affecting multiple toenails, presenting as symmetric transverse depressions of the nail plate, consistent with repeated chemotherapy cycles.

FIGURE 6 | Onychomadesis involving both fingernails and toenails, due to severe chemotherapy-induced matrix arrest.

Because nail matrix cells are a continuously proliferating tissue, they are particularly susceptible to antimitotic drugs, resulting in a transient interruption of nail production that becomes visible weeks later as the nail grows distally [4, 10].

In paediatric oncology, classic chemotherapeutic regimens containing cyclophosphamide, anthracyclines, vincristine and antimetabolites have been repeatedly associated with Beau's lines and occasionally with onychomadesis [4, 16]. These agents are commonly administered for acute lymphoblastic leukaemia, acute myeloid leukaemia and other childhood malignancies [1, 16].

Clinically, Beau's lines appear as transverse depressions affecting several nails simultaneously and are usually symmetrical (Figure 5), supporting a systemic aetiology [18, 19]. When the matrix arrest is more profound, nail growth stops completely and proximal nail plate separation occurs, leading to onychomadesis (Figure 6) and eventual shedding of the nail [4, 18, 19].

The lesions typically appear several weeks after chemotherapy cycles due to the delay between matrix injury and emergence of the affected plate segment [4, 10]. Multiple fingernails are more commonly involved than toenails because of their faster growth rate, although pressure-related toenail involvement may occur

FIGURE 7 | Nail fragility in a 15-year-old patient undergoing chemotherapy for a haematologic malignancy, showing brittle nails with lamellar exfoliation affecting multiple toenails.

in active children [10]. Repeated chemotherapy cycles may produce multiple parallel depressions corresponding to each treatment course, allowing retrospective correlation with therapy timing [10, 12].

Despite their alarming appearance, these nail alterations are usually asymptomatic, although partial shedding may cause discomfort and risk of secondary infection [4].

2.5 | Nail Fragility

Nail fragility refers to increased brittleness of the nail plate characterized by splitting, softening, lamellar exfoliation into fine horizontal layers (onychoschizia) or longitudinal fissuring (onychorrhexis) due to impaired nail plate integrity (Figure 7) [9, 30]. In paediatric oncology patients, nail fragility is a recognized consequence of conventional chemotherapy because antineoplastic agents target rapidly proliferating nail matrix keratinocytes responsible for nail plate production [12, 17]. Damage to matrix keratinization alters intercellular adhesion of corneocytes and produces a thinner, softer and more breakable nail plate, which becomes prone to fissuring and layering [12, 30]. This toxicity occurs in multiple nails simultaneously because the drug effect is systemic rather than traumatic [10, 30].

Conventional chemotherapeutic agents commonly administered in childhood malignancies, including alkylating agents, antimetabolites and anthracyclines, have all been associated with nail plate dystrophy and fragility [16, 17]. These drugs are widely used in acute lymphoblastic leukaemia, acute myeloid leukaemia and lymphomas, explaining why brittle nails may be encountered during treatment in children [1, 16]. Because children have faster nail growth, manifestations may appear earlier but also resolve more rapidly compared with adults [16].

Nail fragility may also be exacerbated by micronutrient deficiencies, which are common in children with cancer because of reduced oral intake, malabsorption, treatment-related gastrointestinal toxicity and increased metabolic needs [31, 32]. Biotin deficiency has been associated with brittle nails, iron deficiency

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with koilonychia, and zinc or selenium deficiency may contribute to nail dystrophy, reduced nail growth and structural nail alterations [33, 34].

These conditions are usually asymptomatic but may cause functional discomfort during daily activities or minor pain when fissures deepen [30]. Because the pathology results from temporary matrix dysfunction, nails progressively normalize after treatment completion as new keratin is produced [10]. Complete recovery generally occurs within months, depending on nail growth rate, without permanent damage [9].

3 | MEK Inhibitors

MEK inhibitors are targeted anticancer agents that block the mitogen-activated protein kinase (MAPK) signalling cascade through inhibition of MEK1 and MEK2 kinases, key downstream mediators of RAS-RAF signalling controlling proliferation and differentiation [2, 35].

Activation of the MAPK pathway is frequent in paediatric tumours, making MEK inhibition an effective therapeutic strategy in several childhood neoplasms [36, 37]. The most established paediatric indication is neurofibromatosis type 1 associated plexiform neurofibromas, in which selumetinib, but also recently approved drugs such as binimetinib and mirdametinib, induce tumour shrinkage and functional improvement [36, 38–40]. MEK inhibitors are also used in progressive low-grade gliomas and other MAPK-activated tumours, including histiocytic disorders and BRAF-altered central nervous system tumours [41, 42].

Because the MAPK pathway regulates epidermal growth and adnexal structures, its inhibition produces characteristic cutaneous toxicities affecting skin, hair and nails [43, 44]. Frequent adverse effects include acneiform eruption, xerosis, pruritus, mucositis and oedema, but chronic paronychia represents one of the most distinctive toxicities in children [45, 46]. MEK inhibitors-induced paronychia appears to be more frequent in paediatric patients than in adults, possibly because children are more exposed to repeated mechanical trauma of the nail unit through sports activities, tight footwear, nail biting or periungual manipulation [47].

Periungual toxicity usually develops after several weeks or months of therapy rather than immediately after treatment initiation [37, 46]. The earliest manifestation is mild erythema and tenderness of the lateral nail folds, often initially misinterpreted as traumatic irritation [9, 45]. Progressive oedema and painful fissuring appear, particularly around the great toes exposed to pressure from footwear [48, 49]. Multiple digits are almost always involved, and bilateral symmetry is common [37, 46]. Inflammation may fluctuate with trauma and physical activity and is frequently exacerbated by sports participation in children [9, 48].

Over time, granulation tissue develops at the lateral nail folds, forming friable bleeding neoformations resembling pyogenic granulomas (Figure 8) [9, 50, 51]. These lesions may bleed easily and could become secondarily colonized by bacteria, leading to pain and functional limitation [37, 45].

Onycholysis and nail plate dystrophy may occur in chronic cases due to persistent inflammation of the nail apparatus [9, 46].

FIGURE 8 | Paronychia affecting multiple toenails with associated periungual pyogenic granulomas in a patient with neurofibromatosis type 1 treated with selumetinib. Chemical matricectomy of the lateral nail horns was performed on the right great toe, leading to clinical remission.

FIGURE 9 | Beau's lines of the toenails in a patient undergoing treatment with tyrosine kinase inhibitors.

The clinical course is chronic and relapsing during therapy and improves slowly after dose reduction or treatment interruption [37, 38].

MEK inhibition disrupts keratinocyte proliferation and epidermal barrier integrity, leading to fragility of periungual epithelium [2, 35]. Microtrauma induces an inflammatory response and abnormal wound healing with vascular proliferation, explaining the formation of pyogenic granulomas [35, 46]. The mechanism closely resembles EGFR inhibitor-induced paronychia, supporting shared management strategies [15, 52].

Correct grading of periungual toxicity is essential because it guides therapeutic escalation and helps avoid unnecessary interruption of oncologic therapy [15, 53].

The Severity of Paronychia Oncologic Treatment (SPOT) score is a dedicated clinical scoring system developed to quantify oncologic treatment–related paronychia based on objective and subjective parameters [53]. The score evaluates four domains: erythema, oedema, discharge/crusting and pain, each graded

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from absent to severe, allowing a reproducible clinical assessment [53]. This tool is particularly useful in paediatric patients because functional limitation and pain rather than lesion size determine impact on quality of life [45, 53].

The Multinational Association of Supportive Care in Cancer (MASCC) grading scale classifies paronychia severity based on symptoms and functional impairment [15]. Although it was designed for EGFR inhibitors, this grading is useful in paronychia induced by MEK inhibitors, given the similarity in toxicity and the underlying pathogenic mechanism. Grade 1 corresponds to mild periungual erythema or swelling without pain or functional limitation; Grade 2 includes painful inflammation interfering with instrumental activities and may be associated with granulation tissue; and Grade 3 indicates severe pain, marked inflammation, interfering with daily activities or secondary infection that requires systemic therapy or treatment interruption [15].

Using structured grading systems allows clinicians to escalate treatment progressively rather than prematurely discontinuing MEK inhibitors [9, 38, 52].

4 | BRAF Inhibitors

BRAF inhibitors are targeted agents acting on the MAPK pathway and are increasingly used in paediatric oncology for BRAF V600E mutated tumours, including Langerhans cell histiocytosis, low-grade gliomas and other refractory central nervous system neoplasms [54, 55]. Nail changes associated with BRAF inhibitors used as monotherapy appear to be uncommon in children and are reported much less frequently than MEK inhibitor–related toxicities. Dermatologic adverse events include keratosis pilaris–like eruption, xerosis, photosensitivity, maculopapular rash and panniculitis, while nail changes are less frequent but recognized, especially paronychia and nail fragility [2, 44, 54, 56].

5 | Multi-Tyrosin Kinase Inhibitors (TKIs)

TKIs are increasingly used in paediatric oncology for both haematologic and solid malignancies, including chronic myeloid leukaemia, Philadelphia chromosome–positive acute lymphoblastic leukaemia, gastrointestinal stromal tumours, and other kinase-driven neoplasms [4, 57]. Nail toxicities in children receiving TKIs reflect the inhibitory effects on rapidly proliferating nail matrix keratinocytes and periungual tissues and may involve the nail plate, nail bed and periungual tissue [9, 10].

The most frequently reported nail alterations include melanonychia, leukonychia, nail fragility, onycholysis, Beau's lines (Figure 9), splinter haemorrhages and paronychia, sometimes associated with periungual pyogenic granulomas [4, 10]. Most nail changes are reversible after dose reduction or discontinuation, and early dermatologic assessment helps maintain treatment adherence and quality of life in paediatric patients [1, 10].

6 | Mammalian Target of Rapamycin (mTOR) Inhibitors

mTOR inhibitors, including sirolimus, everolimus and temsirolimus, are increasingly used in paediatric oncology for conditions such as subependymal giant cell astrocytoma in tuberous sclerosis complex, solid tumours, vascular anomalies and refractory malignancies [44, 58]. Nail toxicities associated with mTOR inhibitors predominantly involve the periungual tissues rather than the nail plate [10, 58, 59]. The most characteristic manifestation is painful paronychia, often bilaterally affecting the great toes and developing several weeks to months after treatment initiation [9, 60]. Clinically, patients present with erythema, oedema, tenderness of the lateral nail folds, and sometimes serous or purulent discharge [60]. Periungual pyogenic granulomas may develop in more advanced cases [4, 60].

The pathogenesis is thought to involve impaired keratinocyte proliferation and altered wound healing due to inhibition of the PI3K/AKT/mTOR pathway, leading to fragile periungual epithelium susceptible to inflammation [2, 59].

Management is mainly supportive and parallels strategies used for MEK inhibitor–induced paronychia. In refractory or severe cases, dose reduction may be necessary, often resulting in gradual regression of the lesions [60].

7 | Anaplastic Lymphoma Kinase (ALK) Inhibitors

ALK inhibitors, such as crizotinib, alectinib and lorlatinib, are used in paediatric oncology primarily for ALK-driven malignancies including neuroblastoma and anaplastic large cell lymphoma, as well as selected inflammatory myofibroblastic tumours [2, 7]. In paediatric clinical trials, ALK inhibitors have shown a relatively favourable dermatologic safety profile compared with other targeted therapies [2]. Nail toxicities associated with ALK inhibitors appear to be rare, particularly in paediatric patients, and have been reported mainly in adults, with manifestations ranging from paronychia and onycholysis to broader nail bed disorders [2, 7].

8 | Management

8.1 | Melanonychia

Management of melanonychia of multiple digits consists mainly of observation and parental reassurance, with dermoscopic documentation when needed to avoid unnecessary biopsy [9, 12, 61, 62]. Specific treatment is not required because pigmentation reflects melanin deposition within the growing nail plate rather than permanent matrix damage [4, 10].

8.2 | Leukonychia

No specific treatment of leukonychia is required, and management consists mainly of reassurance and monitoring, as the condition is benign [4, 9]. Mees' lines progressively grow out with the nail plate, whereas Muehrcke's lines disappear after cessation of chemotherapy [10, 26].

8.3 | Onycholysis

Management of onycholysis is mainly conservative and relies on physical and protective measures, including cutting the

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onycholytic nail plate, protection of the exposed nail bed, avoidance of trauma, repetitive friction and prolonged moisture, and antiseptic soaks to prevent secondary infections [9]. Chemotherapy discontinuation is rarely required [4, 9].

Haemorrhagic onycholysis induced by taxanes requires topical corticosteroids associated with antibiotics to promote repair of the eroded nail bed and reduce pain [9, 12, 63].

After completion of treatment, the nail gradually reattaches as a new plate grows from the matrix, and complete recovery usually occurs over several months [10].

8.4 | Onychomadesis and Beau's Lines

Management of onychomadesis and Beau's lines is conservative and consists of reassurance, protection from trauma, and hygiene measures to prevent bacterial colonization [9, 12]. Chemotherapy modification is rarely required because the condition is benign and self-limited [10]. Normal nail growth resumes after recovery of the nail matrix, and complete resolution occurs progressively over months as the damaged plate grows out or is replaced [10, 19].

8.5 | Nail Fragility

Management of nail fragility is supportive and aimed at protecting the weakened nail plate rather than modifying chemotherapy [9, 12]. Patients should avoid repeated trauma, nail biting, manicuring and prolonged water exposure while keeping nails short and regularly filed [9, 12, 64]. Topical emollients and protective nail lacquers may improve plate cohesion and reduce splitting [9, 30].

In children with persistent or disproportionate nail fragility, nutritional status and selected micronutrient deficiencies should be considered, especially in the presence of malnutrition or other cutaneous signs of deficiency [31–34].

Practical preventive and supportive recommendations for patients, caregivers and clinicians are summarized in Table 1.

8.6 | Paronychia and Periungual Pyogenic Granulomas

Management must be proactive and multidisciplinary to avoid treatment discontinuation [38, 52]. Patients who take drugs that put them at risk of developing paronychia, such as MEK inhibitors, should wear comfortable shoes, keep nails short, avoid nail trauma, onychophagia and onychotillomania [9, 12, 49]. Daily antiseptic soaks reduce colonization [45, 49, 52].

Topical corticosteroids under occlusion film and antiseptics are first-line therapy [37, 52]. Topical antibiotics or antifungals are added if infection is suspected [45, 48]. In addition, some topical antibiotics such as mupirocin are extremely useful as local anti-oedema agents [65].

Systemic antibiotics should not be considered first-line therapy for MEK inhibitor–related paronychia and should be reserved for selected cases with severe inflammation or suspected secondary infection. Oral doxycycline may be considered only in children older than 8 years because tetracyclines are generally contraindicated below this age, and their efficacy in paronychia management is limited. In younger children, or when tetracyclines are not appropriate, azithromycin may represent a safer alternative because of its antimicrobial and anti-inflammatory properties [47, 52, 66].

TABLE 1 | Practical advice for patients, caregivers and clinicians for prevention and early management of nail toxicities during anticancer therapies in children.

General nail care	• Keep nails short and smoothly trimmed • Avoid nail biting, picking, and aggressive manicure/pedicure • Avoid artificial nails and nail trauma
Prevention	• Wear comfortable, wide shoes to reduce friction and pressure • Maintain good hand and foot hygiene • Dry the periungual area carefully after washing • Consider antiseptic soaks when early periungual inflammation appears
Pigmentary alterations	• Reassure patients and families that melanonychia and leukonychia are often benign, and treatment interruption is rarely needed
Fragility and splitting	• Reduce repeated trauma, prolonged water exposure, and friction • Use emollients and protective nail lacquers when appropriate • Assess micronutrient deficiencies
Onycholysis	• Cut the detached nail plates • Protect the exposed nail bed • Avoid trauma • Assess for bacterial or fungal superinfection if pain or discharge is present
Paronychia	• See Table 2.

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TABLE 2 | Stepwise management of targeted therapies (e.g., MEK inhibitor) related paronychia and periungual pyogenic granulomas.

Grade	Clinical features	Management
Grade 1 (mild)	Mild erythema, oedema, no functional limitation	Hygiene measures, comfortable shoes, nail trimming, antiseptic soaks, topical corticosteroids + topical antibiotics, protective taping
Grade 2 (moderate)	Painful inflammation, pyogenic granulomas and interference with instrumental activities	As Grade 1 + topical beta-blockers, silver nitrate cauterization, curettage, electrocautery
Grade 3 (severe)	Severe pain, infection and interference with daily activities	As Grade 2, + intensive podologic care, systemic antibiotics if needed (doxycycline only if > 8 years; azithromycin as paediatric alternative), possible temporary treatment interruption.
Refractory/recurrent lesions and disabling toxicity	Persistent or relapsing lesions, walking limitation and uncontrolled bleeding	Multidisciplinary management, photodynamic therapy, vascular lasers, partial nail avulsion + chemical lateral matricectomy, dose reduction or temporary MEK inhibitor interruption

Periungual pyogenic granulomas represent the most troublesome manifestation of MEK inhibitors' nail toxicity because they bleed easily and cause significant pain and functional limitation [35, 37]. Management should be stepwise, starting with conservative measures, as in simple paronychia, and escalating to procedural therapy in persistent cases in order to maintain oncologic treatment whenever possible [9, 38].

Together with topical corticosteroids in occlusion associated with topical antibiotics, topical beta-blockers represent first-line therapy for pyogenic granulomas because they inhibit angiogenesis [50, 51, 67]. Beta-blockers, such as propranolol 0.5% gel or cream, applied twice daily, often progressive shrinkage within weeks, especially in the fingernails, and may avoid surgical procedures [50, 68].

Persistent bleeding lesions may require chemical cauterization with silver nitrate, which induces coagulation necrosis of the granulation tissue [9, 35]. Curettage or electrocautery can be performed for bulky lesions causing pain or difficulty walking [9]. Photodynamic therapy may be considered in refractory lesions when repeated regrowth occurs after destruction, although available evidence for targeted therapy–induced periungual pyogenic granuloma-like lesions mainly derives from adult patients. In children, procedural pain may represent an important barrier to its use; therefore, pain-reduction strategies such as treating smaller areas per session, using cold air or cooling spray, oral analgesics after treatment, adjustment of photosensitizer concentration, incubation time or light dose, and child-life support or distraction techniques should be considered [13, 69, 70]. Although no data are currently available on photobiomodulation, this painless technique may be of interest in children because randomized paediatric oncology studies on chemotherapy-induced oral mucositis have shown benefits in pain control and wound healing, with good tolerability and no relevant adverse events [71, 72]. Its use for periungual inflammation or pyogenic granuloma-like lesions remains hypothetical and should be investigated in future studies [71, 72]. Vascular lasers may represent an additional option for refractory lesions. In retrospective paediatric series, both 595-nm pulsed dye laser and 1064-nm long-pulsed Nd:YAG laser showed good efficacy and safety, with high clearance rates and mainly mild transient adverse events. However, these data refer to pyogenic granulomas in general, and evidence for targeted therapy–induced periungual lesions remains limited [73, 74].

Protective taping of the periungual folds is an effective conservative measure to reduce mechanical pressure and friction on inflamed nail folds, particularly useful during walking or sports activity [75]. The tape is applied longitudinally along the lateral nail fold, pulling the periungual skin slightly away from the nail plate in order to decrease penetration of the nail edge into the inflamed tissue [75]. This mechanical separation reduces pain immediately and prevents the formation or recurrence of periungual granulomas [9, 75].

In recurrent pyogenic granulomas, removal of the lateral matrix horn is often necessary to eliminate the mechanical trigger [9]. This procedure should never be the first choice, as multiple digits are often involved, and in patients undergoing active therapy, the lesions may recur. Partial nail avulsion followed by chemical matricectomy using phenol or sodium hydroxide permanently narrows the nail plate and prevents recurrence [9, 12].

Dose reduction or temporary interruption of anticancer therapy is reserved for severe or function-limiting toxicity unresponsive to local treatment [38, 47]. Table 2 summarizes the treatment of paronychia and pyogenic granulomas induced by targeted therapies such as MEK inhibitors.

9 | Conclusion

Nail toxicities represent a frequent yet often underrecognized component of dermatologic adverse events in children receiving both conventional chemotherapy and targeted anticancer therapies. Although rarely life-threatening, these alterations may significantly impair quality of life, limit daily activities and occasionally interfere with optimal oncologic dosing, particularly when pain, inflammation or secondary infection occur [4, 10].

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Conventional cytotoxic agents primarily affect the nail matrix and nail bed, leading to melanonychia, leukonychia, Beau's lines, onychomadesis, onycholysis and fragility, reflecting their antiproliferative effects on rapidly dividing keratinocytes [4, 10]. In contrast, targeted therapies, particularly MEK inhibitors, more commonly induce periungual inflammation, paronychia and pyogenic granulomas, highlighting the critical role of signalling pathways in epidermal and adnexal homoeostasis [4, 11]. Emerging agents, including BRAF, mTOR, ALK and TKIs inhibitors, share partially overlapping patterns of nail toxicity, though generally with lower frequency or severity compared with MEK inhibitors [4, 10].

A multidisciplinary approach involving oncologists, dermatologists, psychologists, and when appropriate, podiatrists is essential to optimize preventive strategies, implement timely topical or systemic therapies, and preserve adherence to lifesaving treatments [4].

Author Contributions

Luca Rapparini and Michela Starace contributed equally to all aspects of the work, including study conception, literature review, manuscript drafting and final revision. Both authors read and approved the final manuscript.

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Ethics Statement

The patients' guardians in this manuscript have given written informed consent to the publication of their case details and photos according to the Declaration of Helsinki principles. Ethical Approval: not applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no data sets were generated or analysed during the current study.

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