Review Article

Systemic Drug-induced Chronic Paronychia and Periungual Pyogenic Granuloma

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Abstract

Paronychia is a painful inflammatory disorder of the nail fold. Periungual pyogenic granuloma – a benign vascular tumor of the capillaries – can develop as a complication of paronychia. We report both, paronychia and periungual pyogenic granuloma, as possible adverse events during systemic drug-therapy. The following groups of systemic drugs have been considered: taxanes, epidermal growth factor-receptor (EGFR) inhibitors, EGFR tyrosine kinase inhibitors, tyrosine kinase inhibitors, inhibitors of MEK/ERK, BRAF inhibitors, CD20 antagonists, vascular endothelial growth factor inhibitors, and retinoids. Recommendations for prevention and treatment are given. Since paronychia is a painful inflammatory disorder that has a negative impact on daily activities, early recognition and adequate treatment improve adhesion to treatment and quality of life.

Keywords: *Adverse events, nail apparatus, paronychia, pyogenic granuloma, systemic drug therapy, treatment*

Introduction

Paronychia is defined as an inflammation of the nail folds of fingers or toes. Paronychia can occur as an acute or chronic disease. Commonly, acute paronychia is a consequence of impaired protective function of skin and caused by bacterial infections. Other etiologies are viruses, fungi, pemphigus vulgaris, or trauma (finger sucking).[1]

Paronychia is considered to be chronic if symptoms of at least 6 weeks duration are reported. In many cases, chronic paronychia is caused by an irritant contact dermatitis [Figure 1].[2]

Pyogenic granuloma (PG), also called lobular capillary hemangioma and teleangiectatic granuloma, is a benign vascular proliferation of skin and mucous membranes that develops after minor trauma [Figure 2]. PG can be a consequence of chronic paronychia. Bleeding and secondary infections are possible complications.[3]

In this review, we will focus on paronychia and PG caused by systemic drugs. Although the onset of the disease may be acute, the course often becomes chronic due to the need to continue the systemic drug treatment.

Taxanes

Taxanes such as docetaxel and paclitaxel are anticancer drugs approved for the treatment of metastatic or locally advanced breast, nonsmall cell lung cancer (NSCLC), prostate, gastric, head-and-neck, and ovarian cancers. These drugs inhibit cancer cell proliferation by supporting the polymerization of tubulin into highly stable intracellular microtubules. Nail changes have been reported in 40–89% during treatments with onycholysis and discoloration as the most common findings. Paronychia is an uncommon adverse event.[4,5]

Epidermal Growth Factor-receptor Inhibitors

Epidermal growth factor-receptor inhibitors (EGFRI) are drugs targeting the extracellular domain of the epidermal growth factor receptor. Cetuximab which is a recombinant IG1 mouse–human chimeric anti-EGFR monoclonal antibody, and panitumumab, is a recombinant, fully human IG2 anti-EGFR monoclonal antibody.

Cetuximab was approved for metastatic colorectal cancer and advanced head-and-neck squamous cell carcinoma.

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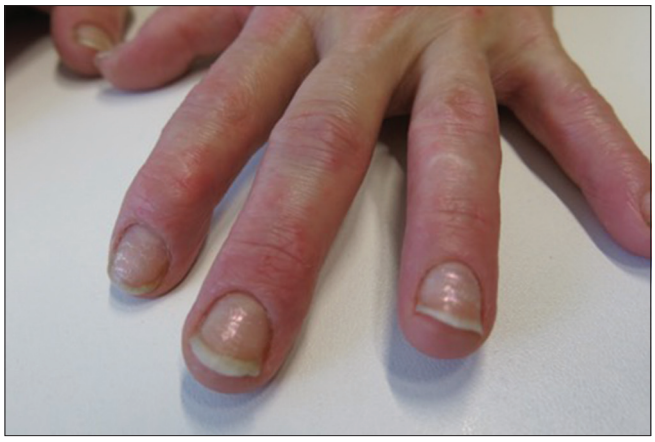

Figure 1: Chronic paronychia due to irritant contact dermatitis with transverse nail plate lines

There is also some evidence that cetuximab has efficacy on other types of nonmelanoma skin cancer as well.[6]

Paronychia is one of the most common cutaneous adverse event during treatment with cetuximab seen in approximately 10% of the patients.[7,8]

Panitumumab was approved as a first-line monotherapy for the treatment of patients with metastatic colorectal cancer and confirmed wild-type KRAS tumor.[9]

Epidermal growth factor-receptor tyrosine kinase inhibitors

Gefitinib [N-(3-chloro-4-fluoro-phenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy) quinazolin-4-amine] inhibits EGFR tyrosine kinase by binding to the adenosine triphosphate (ATP)-binding site of the enzyme (EGFR-TKI). Thereby, the function of the EGFR tyrosine kinase in activating anti-apoptotic Ras signal transduction cascade is inhibited. Gefitinib is used to treat NSCLC, esophageal cancer and breast cancer among other malignancies.[10] Paronychia occurs in about two-third of cancer patients treated with gefitinib.[11] Paronychia has been reported in 13% to 22% of patients as adverse event.[9] Although associated with handicap for hand grip and fine motors skills, paronychia usually does not warrant treatment interruption or cessation [Figure 3].

Erlotinib [N-(3-ethynylphenyl)-6,7-bis (2-methoxyethoxy) 4-quinazolinamine] is an EGFR-TKI that competes with adenosine triphosphate for binding with the intracellular catalytic domain of epidermal growth factor receptor (HER1/EGFR) tyrosine kinase, thereby inhibiting receptor phosphorylation. After receptor binding, the downstream signal transduction is blocked and the tumorigenic effects associated with ligand-dependent and ligand-independent HER1/EGFR activation become inhibited. This drug has been approved for NSCLC and pancreatic cancer.[12] Erlotinib causes paronychia in approximately 28–40% of NSCLC patients.[13,14]

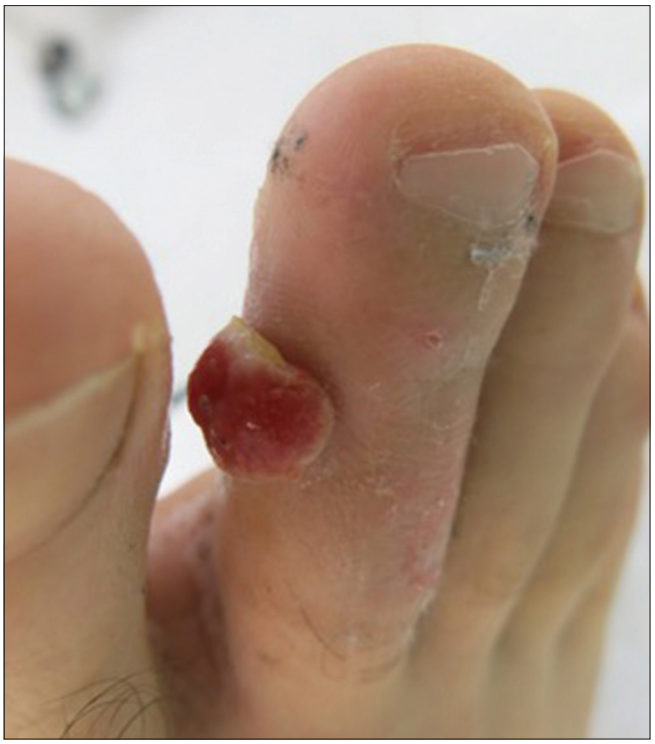

Figure 2: Pyogenic granuloma on the right second toe

Another selective reversible EGFR-TKI is icotinib [4-((3-ethynylphenyl)amino)-6,7-benzo-12-crown-4-quinazoline].[15] Trials have investigated anti-tumor activity and safety in NSCLC.[16] It has been assumed that the shorter half-life of icotinib compared to the two other first-generation EGFRI's is responsible for a reduced percentage of acneiform rash and diarrhea. Detailed data on nail affection by icotinib have not been identified in English literature, but from the basic principle of action, paronchia is a possible adverse event.[17]

Afatinib [(E)-N-[4-(3-chloro-4-fluoroanilino)-7-[(3S)-oxolan-3-yl] oxyquinazolin-6-yl]-4-(dimethylamino) but-2-enamide] is a second-generation EGFR-TKI. It inhibits ErbB signaling by covalently binding to the kinase domains of EGFR, human epidermal growth factor receptor (HER)2, and HER4. This results in an irreversible inhibition of tyrosine kinase autophosphorylation. Afatinib also prevents transphosphorylation of HER3.[18] The drug has been approved for NSCLC but trials have shown anti-tumor activity also in advanced head-and-neck squamous cell carcinoma and urothelial carcinoma.[19,20]

Osimertinib is a third-generation irreversible EGFR-TKI showing inhibitory activity on EGFR *T790M* substitution mutation but less affinity for wild-type EGFR. This could be responsible for minimizing the cutaneous and gastrointestinal toxicities associated with first- and second-generation EGFR-TKI therapy.[21] The drug has been approved for advanced NSCLC. Paronychia has

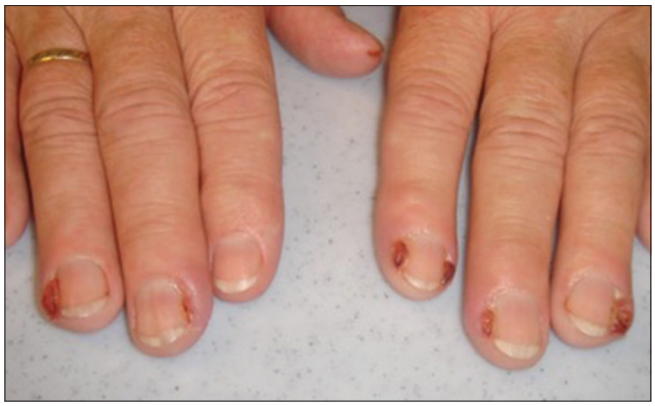

Figure 3: Chronic paronychia in combination with multiple periungual pyogenic granulomas in a 73-year-old female patient treated with panitumumab for signet ring carcinoma of the caecum

been observed in approximately 30–35% of patients treated [Figure 4].[22,23]

Tryosine Kinase Inhibitors

Tyrosine kinase inhibitors (TKIs) target protein tyrosine kinases (PTKs), which exist as transmembrane receptors or as intracellular nonreceptor PTKI. The TKIs are widely used clinically for the treatment of such malignancies as chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GISTs), and renal cell carcinoma.[24]

Imatinib blocks nonreceptor Abelson tyrosine kinase and several other targets. Imatinib-induced periungual PG has been observed occasionally.[25]

MEK- and ERK-inhibitors

The Ras-Raf-mitogen-activated protein kinase (MAPK) cascade is a central effector of cellular differentiation in development and the inappropriate and continuous activation provides a potent promitogenic force and is a very common occurrence in human cancers. MEK- and ERK-inhibitors (MEKI/ERKIs) have been developed and approved for a variety of malignancies including metastatic melanoma.[26]

Cometinib is a potent mitogen-activated protein kinase kinase (MEK) 1/2 inhibitor approved for combination with vemurafenib in metastatic melanoma.[27]

Trametinib is another selective MEK1/2 inhibitor for combined treatment with sorafenib in stage IV melanoma.[28] For both combinations, no significant development of paronychia has been observed.

Selumetinib is a second-generation MEKI. Selumetinib-induced paronychia is characterized by a delayed onset, erythema, swelling, ingrown nail, and resolution upon treatment interruption. The percentage of this adverse event was 9% in one study.[29]

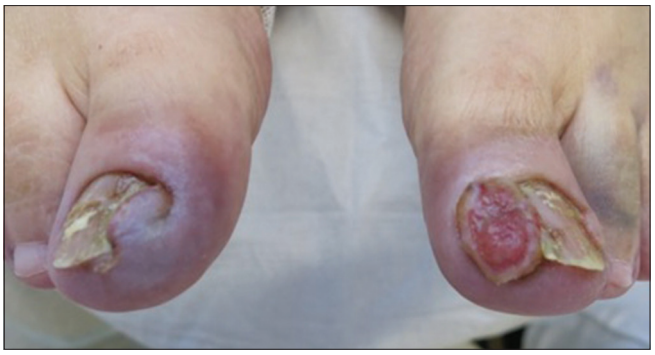

Figure 4: Bilateral severe chronic paronychia and livid discoloration of skin with pyogenic granuloma on the left great toe during palliative nonsmall cell lung cancer treatment with osimertinib

BRAF Inhibitors

Rapidly accelerated fibrosarcoma (RAF), a proto-oncogene product, and BRAF are members of the RAF kinase family. BRAF and RAF are activated by RAS (rat sarcoma). RAF proteins are growth signal transduction protein kinases and their signaling cascade induces gene expression which alters mutagenesis and may also potentiate oncogenesis.[30] BRAF inhibitors (BRAFI) are approved for advanced cancers including cutaneous melanoma.[31]

Vemurafenib is first-in-class small molecule inhibiting of V600 mutant BRAF.[32]

Dabrafenib is another potent and selective BRAF inhibitor with clinical activity against BRAFV600E melanoma, non-BRAFV600E-mutated melanoma, and cancers of other organ systems with the V600K mutation.[33]

Sorafenib is a V600E mutant BRAF and CRAF tyrosine kinase inhibitor with specificity for the ATP-binding pocket of RAF. It also targets the vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR). Sorafenib has been shown to disable the BRAF kinase domain by locking the enzyme in its inactive form and inhibiting the MEK pathway *in vitro* and *in vivo*.[34]

Vemurafenib is known to induce paronychia but trials suggest that this adverse effect is uncommon.[31,35]

Anti-CD20 monoclonal antibody

Rituximab is a chimeric murine/human monoclonal antibody that binds to CD20 on benign and malignant B-lymphocytes leading to a rapid cell depletion. The drug is widely used in hemato-oncology, rheumatology, and dermatology.[36]

Multiple periungual PG's have been observed in a 73-year-old female patient suffering from rheumatoid arthritis treated by rituximab [Figure 5].[37]

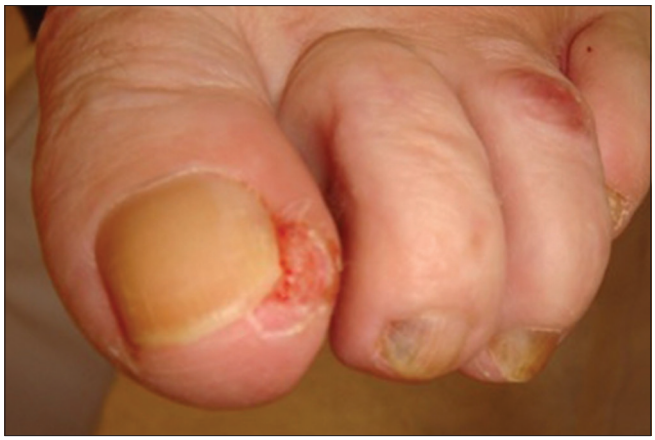

Figure 5: Chronic paronychia with pyogenic granuloma in a patient treated with rituximab for rheumatoid arthritis

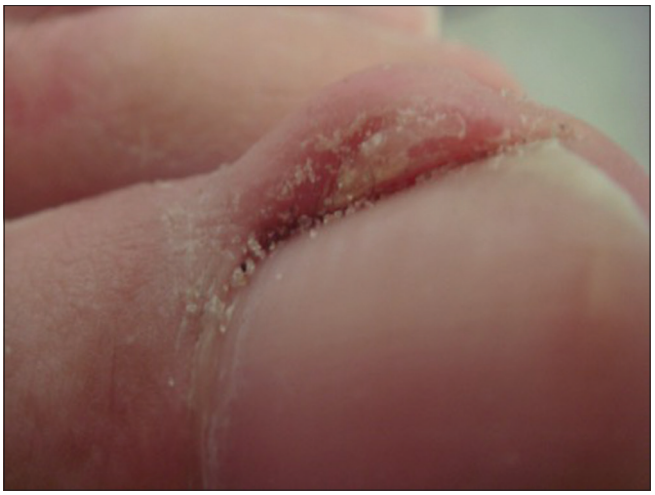

Figure 6: Chronic paronychia of the medial nail fold in a colorectal cancer patient treated with bevacizumab

Vascular endothelial growth factor-inhibitors

The vascular endothelial growth factor (VEGF) signaling pathway plays a dominant role in stimulating tumor angiogenesis. VEGF is overexpressed by most solid tumors and increased levels of VEGEF have also been measured in the circulation of tumor patients.[38]

Bevacizumab is a recombinant, humanized IgG1 monoclonal antibody that blocks VEGF. It has been used successfully in combined treatments of NSCLC, breast cancer, renal carcinoma, and glioblastomas. It is also used intravitreally to combat macular degeneration.[39]

Ranibizumab is a recombinant humanized monoclonal antibody fragment that particularly binds VEGF-A including its cleaved isoform VEGF110. The indication for this compound is macular degeneration. The application is intravitreal.

Adverse events affecting the nail have been reported for bevacizumab but not ranibizumab, what is probably related to dosage and application.[40] However, intravitreal injection of VEGFI can induce PG of the conjunctiva.[41,42]

We observed chronic paronychia in a patient with colorectal cancer treated with bevacizumab-FOLFIRI (5-fluorouracil, folinic acid, irinotecan) [Figure 6].

Retinoids

Isotretinoin is an FDA-approved drug for nodulocystic acne. In a large series of acne patients, chronic paronychia and hypergranulation of the lateral nail folds have been described in four patients.[43,44] Such adverse events are more often seen with etretinate and less with acitretin.[45] In rare cases, PG formation has been observed in patients treated with acitretin.[46,47]

Prevention and Treatment

Patients selected for any of the abovementioned systemic drug therapies should be informed of possible adverse effects to the nail apparatus including paronychia. They should be educated about appropriate nail care (manicure, pedicure) and the regular use of skin barrier creams to protect the nail folds before and during treatment. It is very important to avoid traumatization of the nail structure.[48]

For mild cases, topical solution comprised 2% povidone-iodine in a dimethylsulfoxide vehicle has been shown to be effective in 76% of nails affected within 6 weeks of treatment.[49] The combination of corticosteroid and topical fusidinic acid seems to be superior to topical antibiotics alone.[50]

On chronic paronychia, PG can develop easily. In such patients, surgery or laser-surgery is a treatment option to reduce the time to complete healing.[3]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

1. Durdu M, Ruocco V. Clinical and cytologic features of antibiotic-resistant acute paronychia. J Am Acad Dermatol 2014;70:120-6.
2. Leggit JC. Acute and chronic paronychia. Am Fam Physician 2017;96:44-51.
3. Wollina U, Langner D, França K, Gianfaldoni S, Lotti T,

Tchernev G. Pyogenic granuloma - a common benign vascular tumor with variable clinical presentation: New findings and treatment options. Open Access Maced J Med Sci 2017;5:423-6.
4. Sibaud V, Lebœuf NR, Roche H, Belum VR, Gladieff L, Deslandres M, *et al*. Dermatological adverse events with taxane chemotherapy. Eur J Dermatol 2016;26:427-43.
5. Winther D, Saunte DM, Knap M, Haahr V, Jensen AB. Nail changes due to docetaxel - a neglected side effect and nuisance for the patient. Support Care Cancer 2007;15:1191-7.
6. Wollina U. Update of cetuximab for non-melanoma skin cancer. Expert Opin Biol Ther 2014;14:271-6.
7. Soda H, Maeda H, Hasegawa J, Takahashi T, Hazama S, Fukunaga M, *et al*. Multicenter Phase II study of FOLFOX or biweekly XELOX and Erbitux (cetuximab) as first-line therapy in patients with wild-type KRAS/BRAF metastatic colorectal cancer: The FLEET study. BMC Cancer 2015;15:695.
8. Iwamoto S, Hazama S, Kato T, Miyake Y, Fukunaga M, Matsuda C, *et al*. Multicenter phase II study of second-line cetuximab plus folinic acid/5-fluorouracil/irinotecan (FOLFIRI) in KRAS wild-type metastatic colorectal cancer: The FLIER study. Anticancer Res 2014;34:1967-73.
9. Han van Krieken J, Kafatos G, Bennett J, Mineur L, Tomášek J, Rouleau E, *et al*. Panitumumab use in metastatic colorectal cancer and patterns of RAS testing: Results from a Europe-wide physician survey and medical records review. BMC Cancer 2017;17:798.
10. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, *et al*. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129-39.
11. Takimoto T, Hirashima T, Kobayashi M, Nitta T, Sasada S, Nakamura Y, *et al*. Gefitinib for previously untreated patients with non-small cell lung cancer (NSCLC)--a retrospective study of 12 patients treated in one institution. Gan To Kagaku Ryoho 2005;32:1985-8.
12. Kim TE, Murren JR. Erlotinib OSI/Roche/Genentech. Curr Opin Investig Drugs 2002;3:1385-95.
13. Goldberg SB, Supko JG, Neal JW, Muzikansky A, Digumarthy S, Fidias P, *et al*. A phase I study of erlotinib and hydroxychloroquine in advanced non-small-cell lung cancer. J Thorac Oncol 2012;7:1602-8.
14. Pitarch G, Garde J, Torrijos A, Juárez A, Febrer MI, Camps C. Adverse cutaneous reactions to erlotinib. Actas Dermosifiliogr 2008;99:54-60.
15. Tan F, Shi Y, Wang Y, Ding L, Yuan X, Sun Y. Icotinib, a selective EGF receptor tyrosine kinase inhibitor, for the treatment of non-small-cell lung cancer. Future Oncol 2015;11:385-97.
16. Shi Y, Zhang L, Liu X, Zhou C, Zhang L, Zhang S, *et al*. Icotinib versus gefitinib in previously treated advanced non-small-cell lung cancer (ICOGEN): A randomised, double-blind phase 3 non-inferiority trial. Lancet Oncol 2013;14:953-61.
17. Ni J, Zhang L. Evaluation of three small molecular drugs for targeted therapy to treat non small cell lung cancer. Chin Med J (Engl) 2016;129:332-40.
18. Keating GM. Afatinib: A review of its use in the treatment of advanced non-small cell lung cancer. Drugs 2014;74:207-21.
19. Clement PM, Gauler T, Machiels JP, Haddad RI, Fayette J, Licitra LF, *et al*. Afatinib versus methotrexate in older patients with second-line recurrent and/or metastatic head and neck squamous cell carcinoma: Subgroup analysis of the LUX-Head & Neck 1 trial. Ann Oncol 2016;27:1585-93.
20. Choudhury NJ, Campanile A, Antic T, Yap KL, Fitzpatrick CA, Wade JL 3rd, *et al*. Afatinib activity in platinum-refractory metastatic urothelial carcinoma in patients with ERBB alterations. J Clin Oncol 2016;34:2165-71.
21. Goss G, Tsai CM, Shepherd FA, Bazhenova L, Lee JS, Chang GC, *et al*. Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): A multicentre, open-label, single-arm, phase 2 study. Lancet Oncol 2016;17:1643-52.
22. European Medicines Agency. Tagrisso, INN-osimertinib. Available from: http:// www.ema.europa.eu/docs/de_DE/document_library/.../WC500202022.pdf [Last assessed on 2018 Jan 05].
23. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, *et al*. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 2017 [Epub ahead of print].
24. Hartmann JT, Haap M, Kopp HG, Lipp HP. Tyrosine kinase inhibitors - a review on pharmacology, metabolism and side effects. Curr Drug Metab 2009;10:470-81.
25. Dika E, Barisani A, Vaccari S, Fanti PA, Ismaili A, Patrizi A. Periungual pyogenic granuloma following imatinib therapy in a patient with chronic myelogenous leukemia. J Drugs Dermatol 2013;12:512-3.
26. Avruch J, Khokhlatchev A, Kyriakis JM, Luo Z, Tzivion G, Vavvas D, *et al*. Ras activation of the Raf kinase: Tyrosine kinase recruitment of the MAP kinase cascade. Recent Prog Horm Res 2001;56:127-55.
27. Larkin J, Ascierto PA, Dréno B, Atkinson V, Liszkay G, Maio M, *et al*. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 2014;371:1867-76.
28. Infante JR, Fecher LA, Falchook GS, Nallapareddy S, Gordon MS, Becerra C, *et al*. Safety, pharmacokinetic, pharmacodynamic, and efficacy data for the oral MEK inhibitor trametinib: A phase 1 dose-escalation trial. Lancet Oncol 2012;13:773-81.
29. 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;29:1114-21.
30. Wellbrock C, Arozarena I. The complexity of the ERK/MAP-Kinase pathway and the treatment of melanoma skin cancer. Front Cell Dev Biol 2016;4:33.
31. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, *et al*. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507-16.
32. Heakal Y, Kester M, Savage S. Vemurafenib (PLX4032): An orally available inhibitor of mutated BRAF for the treatment of metastatic melanoma. Ann Pharmacother 2011;45:1399-405.
33. Falchook GS, Long GV, Kurzrock R, Kim KB, Arkenau TH, Brown MP, *et al*. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: A phase 1 dose-escalation trial. Lancet 2012;379:1893-901.
34. McDermott DF, Sosman JA, Gonzalez R, Hodi FS, Linette GP, Richards J, *et al*. Double-blind randomized phase II study of the combination of sorafenib and dacarbazine in patients with advanced melanoma: A report from the 11715 Study Group. J Clin Oncol 2008;26:2178-85.
35. Dika E, Patrizi A, Ribero S, Fanti PA, Starace M, Melotti B, *et al*. Hair and nail adverse events during treatment with targeted therapies for metastatic melanoma. Eur J Dermatol 2016;26:232-9.
36. Onrust SV, Lamb HM, Balfour JA. Rituximab. Drugs 1999;58:79-88.
37. Wollina U. Multiple eruptive periungual pyogenic granulomas

during anti-CD20 monoclonal antibody therapy for rheumatoid arthritis. J Dermatol Case Rep 2010;4:44-6.
38. Ferrara N. Vascular endothelial growth factor as a target for anticancer therapy. Oncologist 2004;9(Suppl 1):2-10.
39. Russo AE, Priolo D, Antonelli G, Libra M, McCubrey JA, Ferraù F. Bevacizumab in the treatment of NSCLC: Patient selection and perspectives. Lung Cancer (Auckl) 2017;8:259-69.
40. Wozel G, Sticherling M, Schön MP. Cutaneous side effects of inhibition of VEGF signal transduction. J Dtsch Dermatol Ges 2010;8:243-9.
41. Jung JJ, Della Torre KE, Fell MR, Teng CC, Freund KB. Presumed pyogenic granuloma associated with intravitreal anti-vascular endothelial growth factor therapy. Open Ophthalmol J 2011;5:59-62.
42. Sagiv O, Piven I, Rosner M. Conjunctival pyogenic granuloma associated with intravitreal bevacizumab injection. Retin Cases Brief Rep 2013;7:291-3.
43. Bigby M, Stern RS. Adverse reactions to isotretinoin. A report from the Adverse Drug Reaction Reporting System. J Am Acad Dermatol 1988;18:543-52.
44. Baran R. Etretinate and the nails (study of 130 cases) possible mechanisms of some side-effects. Clin Exp Dermatol 1986;11:148-52.
45. Badri T, Hawilo AM, Benmously R, Fenniche S, Mokhtar I. Acitretin-induced pyogenic granuloma. Acta Dermatovenerol Alp Pannonica Adriat 2011;20:217-8.
46. Yorulmaz A, Yalcin B. A painful periungual red spot in a patient with onychodystrophy. Skin Appendage Disord 2017;3:67-9.
47. Figueiras Dde A, Ramos TB, Marinho AK, Bezerra MS, Cauas RC. Paronychia and granulation tissue formation during treatment with isotretinoin. An Bras Dermatol 2016;91:223-5.
48. Sibaud V, Robert C, Mateus C, Verschoore M, Charles C, Lanoy E, Baran R. Nail toxicities induced by systemic anticancer agents. Lancet Oncol 2015;16:e181-9.
49. Capriotti K, Capriotti J, Pelletier J, Stewart K. Chemotherapy-associated paronychia treated with 2% povidone-iodine: A series of cases. Cancer Manag Res 2017;9:225-8.
50. Wollina U. Acute paronychia: Comparative treatment with topical antibiotic alone or in combination with corticosteroid. J Eur Acad Dermatol Venereol 2001;15:82-4.