Drug Induced Ulceration of Extremities

17

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17.1 Introduction

Medications are a rare and often ignored cause of limb ulcers. It is presumed that around 1.1% of chronic leg ulcers can be caused by drugs [1]. Limb ulcers can be related to the pharmacological action of drugs or can be the manifestation of drug induced vasculitis or immunological alterations. Early suspicion of drug involvement in the induction of ulcers can result in timely intervention and can prevent considerable morbidity and mortality. Cutaneous ulcers can be observed in complicated cases of drug related immunological conditions such as Stevens-Johnson syndrome (SJS) and drug induced bullous eruptions. Though such association is well documented for some antiepileptics such as phenytoin and antimicrobials like sulphonamides, no drug is completely devoid of risk of hypersensitivity reactions. Discussion of such immunological reactions is hence beyond the scope of this chapter. The aim of the present chapter is to provide a comprehensive review on common drugs implicated in limb ulcers, the possible mechanisms of ulcer development, the phenotypic patterns of drug induced extremity ulcers, their management, and outcomes. Description of such drugs is given individually in the section below as well as in Table 17.1.

17.1.1 Hydroxyurea

Hydroxyurea, also known as hydroxycarbamide, is a hydroxylated version of urea and is used in various haematologic conditions such as chronic myeloid leukaemia, essential thrombocytosis, polycythaemia vera, sickle cell anaemia, and refractory

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Table 17.1 Common drugs implicated in limb ulcers, the associated features, HPE findings and possible mechanisms of ulcer generation

Drug	Used for	Time of onset of ulcers	Affected individuals	Location of ulcers	Associated features	HPE	Tentative mechanism / risk factor	Treatment required	Outcomes
Hydroxyurea	CML, PV, ET	5–6 years	Mainly elderly	Lower limbs (peri malleolar> feet, heel, tibia) > forearms	Disproportionate pain, xerosis, hyperpigmentation of skin, nail discoloration	Epidermal necrosis, dermal fibrosis, and perivascular infiltrates. No evidence of vasculitis or vascular thrombosis	DNA damage and direct toxicity of skin cells, megaloblastic erythrocytes impairing blood flow	Drug discontinuation and symptomatic management	Heal over weeks-months
Warfarin	DVT, PE	3–10 days	Mainly middle aged-elderly females	Fatty areas: Buttocks, thigh, breast, abdomen>distal limbs, toes	Preceded by ecchymotic patch with bluish black discoloration	Thrombosis of dermal venules. No evidence of vasculitis	High starting dose of warfarin without heparin cover. Underlying protein C deficiency/anti thrombin III deficiency/ factor V Leiden mutation precipitates thrombosis by warfarin	Drug discontinuation and alternative anticoagulants such as heparin or NOAC. Surgical debridement is often required for large ulcers	Heal over weeks-months

Heparin	DVT, PE, ACS	5–10 days	–	Injection site: Thigh, abdomen, arms Non injection site: Venous thrombosis of lower limbs	Thrombocytopenia, serum positivity for anti-heparin-PF-4 antibody	Thrombosis of dermal venules, epidermal necrosis or a type III hypersensitivity reaction in the form of vasculitis	Anti-heparin-PF-4 antibody causes platelet aggregation and thrombosis	Drug discontinuation and alternative anticoagulants such as anti-Xa agents or DTI	Heal over weeks-months
Methotrexate	Psoriasis, RA	Days-weeks in psoriasis, 3–10 years in RA	Middle aged-elderly	Lower limbs, hands, elbows, psoriatic skin	Pancytopenia and oral ulcers	–	Inhibition of DNA replication resulting in direct cytotoxicity of epidermal cells. Concomitant use of NSAIDs or steroids hastens the risk.	Drug discontinuation and symptomatic management	Heal over weeks
Propylthiouracil (PTU)	Hyperthyroidism	3–5 years	Mainly adult females	Lower limbs, upper limbs, trunk, and face	Preceded by fever, arthralgia and palpable purpura, p-ANCA and ANA positive, renal involvement common	Vasculitis and perivascular inflammatory infiltrates	Immune mediated small vessel vasculitis secondary to anti-MPO-PTU antibody	Drug discontinuation and symptomatic management. Steroids and immunomodulators such as cyclophosphamide may be required. Surgical debridement is required for large ulcers	Heal over weeks-months

(continued)

Table 17.1 (continued)

Drug	Used for	Time of onset of ulcers	Affected individuals	Location of ulcers	Associated features	HPE	Tentative mechanism / risk factor	Treatment required	Outcomes
Hydralazine	Hypertension, heart failure, PIH	3 years	Elderly females>males	Legs, feet, fingers	Vesiculopustular to ulcerative lesions. Dyspnoea, weight loss, polyarthralgia, GIT and renal involvement. P-ANCA and ANA positive, other antibodies such as anti-histone, anti-dsDNA may also be positive	Leukocytoclastic vasculitis and deposition of IgM, fibrin, and complement protein C3 in the cutaneous blood vessels	Immune mediated small vessel vasculitis secondary to anti-MPO-drug antibody	Drug discontinuation and symptomatic management. Steroids and immunomodulators such as cyclophosphamide may be required.	Heal over weeks-months
Nicorandil	Stable angina	2–4 years	Mainly elderly males	Mainly lower limbs	History of surgery or mild physical trauma may be present. Oral and perianal ulcers	–	Vascular steal phenomenon and accumulation of nicotinic acid metabolites in skin cells	Drug discontinuation and symptomatic management	Heal over weeks-months

Ergotamine	Migraine	Years	Adults	Mainly lower limbs	Claudication and paraesthesia in lower limbs, decreased to absent pulses	–	Constriction of iliac and femoral blood vessels. Cigarette smoking and adrenergic agonists hasten the risk	Drug discontinuation, vasodilators such as nifedipine, prazosin and antiplatelet drugs	Heal over weeks-months

ACS acute coronary syndrome, *ANA* antinuclear antibody, *CML* chronic myeloid leukaemia, *DNA* deoxyribonucleic acid, *DTI* direct thrombin inhibitors, *DVT* deep venous thrombosis, *ET* essential thrombocytosis, *GIT* gastrointestinal tract, *HPE* histopathologic examination, *MPO* myeloperoxidase, *NOAC* novel oral anticoagulants, *NSAIDs* non-steroidal anti-inflammatory drugs, *p-ANCA* perinuclear-anti neutrophil cytoplasmic antibody, *PE* pulmonary embolism, *PF-4* platelet factor-4, *PIH* pregnancy induced hypertension, *PV* polycythaemia vera, *RA* rheumatoid arthritis

hyper eosinophilia. Given at the therapeutic dose of 500–1000 mg twice a day, the drug is known to cause mucocutaneous adverse effects (AEs) such as xerosis, hyperpigmentation of skin, discolouration of nails, and cutaneous ulcers. Numerous case reports and a large case series ($n = 41$) of hydroxyurea associated limb ulcers exist in literature [2–6]. Around 12% patients on hydroxyurea therapy may develop cutaneous ulcers [7]. Ulcers occur after years of therapy (mean time of onset ≈ 5 years) and have been reported as early as after 6 months of drug intake. Elderly are commonly affected, with no sex wise differences. Ulcers can be single or multiple and are typically located on the peri malleolar area, lower half of the anterior aspect of tibia, feet, and heel (Fig. 17.1). In rare cases, the forearm can also be involved [8]. Well demarcated margins of ulcers with surrounding erythema, cutaneous atrophy, and associated hyperpigmentation of skin are the presenting features. Severe pain out of proportion to the ulcer is another typical complaint. Ulcers can be preceded by trivial trauma such as a minor scratch and are often refractory to conservative treatment unless the drug is discontinued. Secondary bacterial infections and cellulitis may develop in undiagnosed cases [2, 3]. Histopathologic examination (HPE) of ulcer shows epidermal necrosis, dermal oedema and fibrosis, hyalinization of vessels and perivascular inflammatory infiltrates, with no evidence of vasculitis [3, 7]**.** Ulcers heal over a period of weeks–months with drug discontinuation and symptomatic management. Though the mechanism behind the ulcerogenic state is not fully clear, the drug is known to impair DNA synthesis thereby causing cell cycle arrest of rapidly proliferating cells such as the keratinocytes. The drug also causes megaloblastic changes in erythrocytes leading to their poor deformability, impairing cutaneous blood flow.

17.1.2 Anagrelide

Anagrelide is another drug used in the treatment of myeloproliferative disorders and thrombocythemia. The drug acts by inhibiting phosphodiesterase (PDE) and increasing c-AMP inside platelets and vascular smooth muscle cells. It interferes

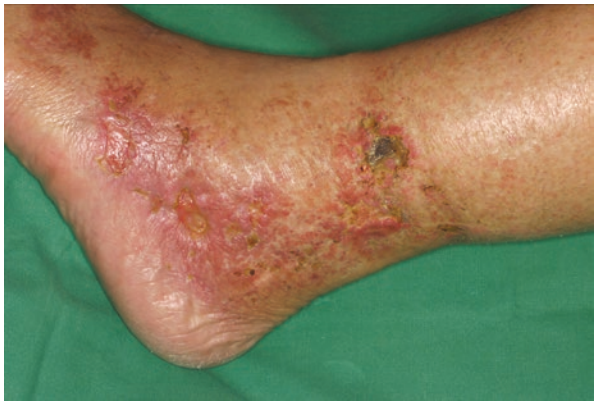

Fig. 17.1 Hydroxyurea induced lower limb ulceration

with maturation of megakaryocytes to platelets and thus decreases platelet count. Common AEs of anagrelide are related to the pharmacological action and include headache, hypotension, and tachycardia. The drug can also cause mucocutaneous AEs such as xerosis and hyperpigmentation and in rare cases, cutaneous ulcers. Ulcers are generally located on lower limbs, mainly around the lateral malleolar area and are painful [9, 10]. Time of onset varies from 6 weeks to 1 year. Ulcers are refractory to symptomatic therapy including surgical debridement and heal only following drug discontinuation. Whether pathogenesis of ulcer development is related to the thrombotic milieu of underlying disorders or is solely related to drug, needs further understanding [9, 10].

17.1.3 Warfarin

Warfarin is an oral anticoagulant used for the prevention and treatment of thromboembolic states such as deep venous thrombosis and pulmonary embolism and in the prophylaxis against stroke in patients of atrial fibrillation. Bleeding is the most common AE of the drug. Rarely, the drug can cause cutaneous disturbances in the form of dermatitis, urticaria, maculopapular lesions, and skin necrosis. The exact incidence of warfarin induced skin necrosis (WISN) is not known due to rarity of the event but is thought to affect 0.01–0.1% of drug users [11]. The condition starts within 3–10 days of warfarin intake and is common in middle aged–elderly, obese women. Individuals with deficiency of protein C, protein S, factor V Leiden mutation, antithrombin III deficiency and those with anti-phospholipid antibodies are particularly vulnerable to this disabling condition [12, 13]. Loading with high dose of warfarin without pre-treatment with heparin is another potential risk factor. Classically affected areas are the fatty regions such as of breast, abdomen, thighs, and buttocks. Penile involvement may occur in men. Uncommonly, distal parts of lower limbs and toes can be affected. WISN may start as paresthesias in the affected area followed by appearance of erythema and ecchymotic patch (Fig. 17.2). The lesion is purplish to begin with, is followed by a blue-black discolouration and often, is misdiagnosed as haematoma. Appearance of haemorrhagic bullae often leads to permanent full thickness damage of the skin and exposure of underlying muscles and tendons. HPE of lesion shows thrombosis of venules and fibrin deposits in the cutaneous vessels. Vasculitis and inflammatory infiltrates are less common. Treatment requires warfarin discontinuation and administration of systemic anticoagulants such as heparin or novel oral anticoagulants like dabigatran along with optimal wound care. Purified protein C concentrates can be given but their availability and high cost are the limiting factors. Small lesions may heal with this conservative approach, but surgical debridement and grafting is usually required for large lesions. Since benefits of drug overweigh the risk of WISN, resumption of drug at low dose may be tried in future if no alternatives are available. This should always be preceded by adequate heparin coverage [11].

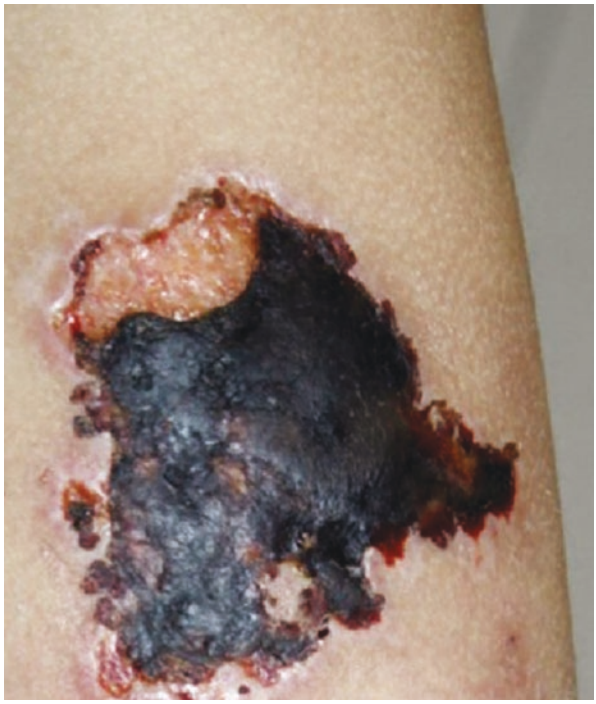

Fig. 17.2 Warfarin induced skin erythema, necrosis, and ulceration

17.1.4 Heparin

Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are systemic anticoagulants used in the prevention and treatment of venous thrombosis, in the immediate management of acute coronary syndromes and to prevent coagulation in extracorporeal circuit in patients undergoing dialysis. Bleeding is their most common AE. The drugs in rare cases can cause thrombocytopenia also known as heparin induced thrombocytopenia (HIT). Around 0.5–1% patients on UFH may be complicated by HIT and the incidence rate is further low (0.2–0.3%) with LMWH. Major morbidity in HIT is not because of thrombocytopenia but is rather accounted by thrombosis, defined better as heparin induced thrombocytopenia and thrombosis (HITT). Thrombocytopenia is usually not severe, and platelet fall below 20,000/μL is uncommon. IgG antibodies induced by heparin-platelet factor-4 (PF-4) complex activate the platelets and lead to the hypercoagulable state. Thrombosis classically develops within 5–10 days of heparin use, is common in post-surgery period and predominantly involves veins than arteries. Local skin sites such as of abdomen, thigh, and arms are usually affected. Lesions can be erythematous to begin with and can be necrotizing to non-necrotizing. Involvement of distant sites is not uncommon. Fatalities due to stroke and myocardial infarction can occur in missed cases. Bilateral deep venous thrombosis developing during heparin therapy is a strong clue towards the development of HITT and if undiagnosed leads to potential sequelae in the form of venous gangrenes. Splanchnic, cerebral, and adrenal

veins are some other atypical sites involved in HITT. Diagnosis of HITT is mainly clinical and supported by four Ts (**T**hrombocytopenia, **t**hrombosis, **t**iming, and o**t**her causes ruled out). Anti-heparin-PF-4 antibody is present in majority of cases. In the event of suspicion of HITT, heparin should be discontinued, and alternative anticoagulants should be initiated for the treatment of thrombus and prevention of its progression. Direct thrombin inhibitors such as bivalirudin and dabigatran, and anti-Xa agents such as fondaparinux are preferred in this setting. Other emerging therapies include oral factor Xa inhibitors such as rivaroxaban and apixaban. Warfarin can also be given but its use should be preceded by direct thrombin inhibitors as possible aggravation of skin necrosis can occur in undiagnosed protein C deficiency states. HPE of skin lesions may show epidermal necrosis, thrombosis of dermal vessels or features of type III hypersensitivity reaction such as vasculitis, induced by heparin-PF4-antibody immune complexes. In the event of occurrence of HITT, reinstitution of heparin in future can be allowed for short term such as to cover the peri-operative need, if platelet activating antibodies are undetectable in serum. This should be followed by careful clinical monitoring as well as monitoring of platelet count for at least 10 days post-last dose of heparin as possibility of occurrence of delayed HITT exists [14–16].

17.1.5 Ergot Compounds

Ergot compounds such as ergotamine and ergotoxine are used in the treatment of migraine attacks. The compounds act as partial agonist at adrenergic α and serotonergic receptors resulting in vasoconstriction. Claviceps purpurea, a fungus growing on grains such as rye is the source of natural ergot compounds. Attacks of ergot poisoning or "ergotism" in the form of limb gangrenes and convulsions were witnessed in the Middle Ages with some reports occurring in the nineteenth century and few in 1950s in France. Following the association of fungus with these symptoms, cases of ergotism have declined. Rare cases of ergot compound toxicity in the form of limb ischaemia and ulcers over the lower limbs are reported with ergotamine intake [17]. Chronic consumption of ergotamine over years for migraine attacks is a consistent feature in these reports. In sensitive individuals, however, dose as low as 2 mg can provoke significant ischaemia [17–19]. Constriction of iliac and femoral blood vessels is evident in early phases, followed by more severe involvement of distal blood vessels. Cases resolve with discontinuation of ergot preparation and administration of vasodilators such as prazosin and nifedipine, and antiplatelet drugs such as aspirin.

17.1.6 Methotrexate

Methotrexate associated skin ulcers were described initially in patients of psoriasis. Ulcers can involve the psoriatic skin or can arise de novo over the uninvolved skin. The dose of methotrexate has varied from 7.5 mg–25 mg/week in reported cases.

When involving the psoriatic skin, ulcers arise usually within days-weeks of start of therapy while the time of onset is variable when non psoriatic skin is involved. Ulcers heal successfully within weeks of drug discontinuation [20].

Cutaneous ulcers with methotrexate have also been reported in nonpsoriatic conditions such as rheumatoid arthritis (RA) particularly in old age patients. The onset of ulcers is often delayed, varying from 3–10 years of therapy [21, 22]. Lower limbs, hand, and elbows are the typical sites involved. Patients may have concomitant oral ulcers and pancytopenia and may have other contributory conditions such as diabetes, cardiovascular diseases, renal insufficiency, and haematological malignancies. The development of ulcers is hastened with concomitant intake of steroids, biologicals, and non-steroidal anti-inflammatory drugs (NSAIDs) [21]. Foot ulcers as early as within days have been reported with a low 5 mg dose of methotrexate consumed erroneously on daily basis [23]. Treatment requires drug discontinuation and symptomatic management, and significant healing occurs over weeks. The mechanism of ulcer induction by methotrexate has been hypothesized to be related to the pharmacological inhibition of folate synthesis and DNA replication. Rapidly proliferating cells such as of skin are consequently affected resulting in cutaneous atrophy and ulceration.

17.1.7 Leflunomide

Leflunomide is another dug with disease modifying roles in immune conditions such as RA and psoriasis. Diarrhoea and liver toxicity are its common AEs. Mucocutaneous adverse effects such as rashes and alopecia are also not uncommon. Cutaneous ulcers on lower limbs and forearms have been reported mainly in elderly females after months of therapy with leflunomide. The drug inhibits dihydroorotate dehydrogenase enzyme involved in pyrimidine synthesis as well as blunts the action of growth factors such as epidermal derived growth factor (EDGF). Both mechanisms can explain the ulcerogenic potential of drug. HPE done in limited cases has shown evidence of inflammation in dermis and subcutaneous tissue with necrosis of collagen fibres and presence of granulation tissue. Granulomas with giant cells may also be seen. Following drug discontinuation, healing starts, albeit slowly and full healing may require a span of 8–18 months. Leflunomide has active metabolite with a long t-half of 1–4 weeks. The drug activity may last for months, explaining the delayed healing process [24, 25].

17.1.8 Sedative Use and Limb Ulcers

Sedatives such as members of barbiturate class, benzodiazepines, Z- compounds like zolpidem, antihistaminics like diphenhydramine, and other drugs with sedative action such as opioids, all have been linked with ulcers on the lower limbs. Ulcers are generally of pressure ulcer type and located on the lower back or interior aspects

of knees. In one study, nearly 45% elderly patients with pressure ulcers were using sedative drugs. Furthermore, the risk of severe ulceration was observed to be five times higher in patients using sedatives versus those not using sedatives [26].

Opioid abuse: Opioids such as pentazocine have been linked with cutaneous ulcers [27, 28]. Ankles, tibial sites, and cubital fossa are the typical sites involved and the time of onset can vary from 10 days to years of drug abuse. Ulcers start with bullous lesion and upon rupture expose deeper tissues such as muscles. Ulcers have a necrotic base, hyperpigmented margins, and surrounded by indurated skin. Thrombophlebitis, multiple scars, and venous sclerosis may also be evident. Other associated features include non-pitting oedema of hands and feet, typically known as the puffy hand syndrome and muscle contractures. HPE findings include epidermal necrosis, perivascular infiltrates of neutrophils and lymphocytes in dermis, vasculitis, and neutrophilic abscesses. Typical location of ulcers at easily accessible sites, difficulty in accessing the peripheral veins, presence of hand oedema and muscle contractures are some of the potential clues of pentazocine abuse leading to ulcers. Urinary pentazocine screening should be done but can be negative if patient has not taken the drug recently. Though conservative management has been tried successfully by some, excision followed by grafting is required in majority of the cases [27]. Drug discontinuation should be done cautiously with vigilance for withdrawal features. Psychiatry referral should be done for counselling and de-addiction therapies.

17.1.9 Propylthiouracil

Propylthiouracil is used in the management of hyperthyroidism. Common AEs of this drug include hepatitis and cutaneous reactions. A characteristic but uncommon AE is agranulocytosis. In rare cases (<1/10000), the drug is known to cause vasculitis [29]. Case reports of pyoderma gangrenosum also exist with PTU [30]. Vasculitis occurs predominantly in females (F/M: 8/1) and after years of therapy (median duration of therapy≈ 42 months). Systemic symptoms such as fever, rash, and arthralgia are the initial manifestations. Rash starts as palpable purpura and patchy lesions (Fig. 17.3). Gradually, full thickness of skin is involved, lesions become necrotic and widespread. Common sites are lower limbs and upper limbs. Trunk and face may also be affected. Patients usually test positive for perinuclear-anti neutrophilic cytoplasmic antibodies (p-ANCA) and antinuclear antibodies (ANA). Concomitant renal involvement is seen in more than 50% of cases. HPE of ulcers shows evidence of vasculitis and perivascular inflammatory infiltrates. Significant recovery occurs with drug discontinuation and administration of steroids with or without immunomodulators. Large ulcers may necessitate surgical debridement and grafting. Nearly 8–9% patients may succumb to the disease because of renal involvement and sepsis [29]. A high index of suspicion for vasculitis should be kept in patients on PTU developing early signs of cutaneous involvement. In the event of vasculitis, the drug should never be reintroduced.

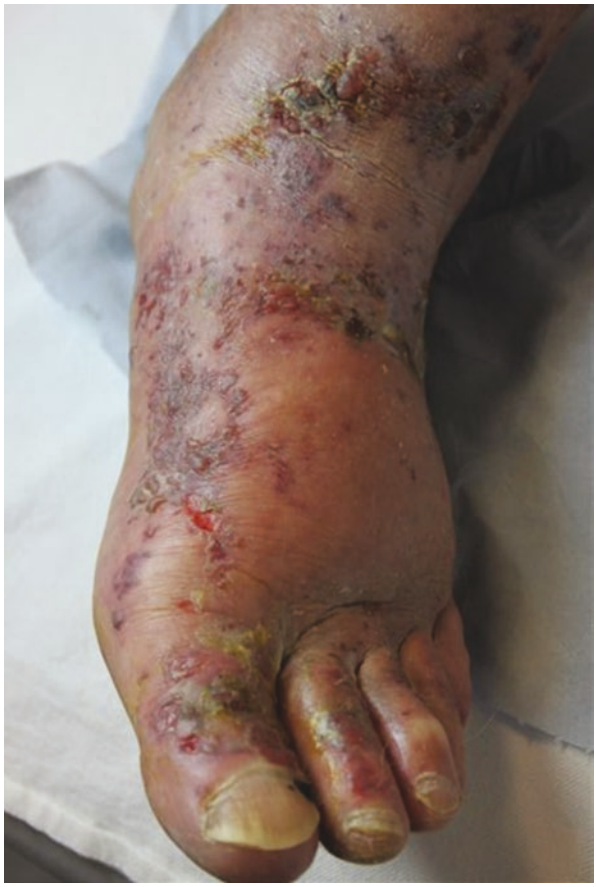

Fig. 17.3 Propylthiouracil associated vasculitis and patchy skin lesions

17.1.10 Hydralazine

Hydralazine is an arteriolar vasodilator used in the treatment of hypertension, pregnancy induced hypertension, and congestive heart failure. Hypotension, tachycardia, and headache are its common AEs. Uncommonly and after years of therapy, the drug is implicated in immunological conditions such as drug induced lupus and ANCA positive vasculitis. Females, older age, and increased dose of hydralazine are the traditional risk factors of these disorders. Vasculitis manifests as dyspnoea, weight loss, rash, and polyarthralgia. Rash is vesiculopustular to ulcerative and commonly involves legs, feet, and fingers. Among other systemic features, mucosal involvement of airways and gastrointestinal tract and rapidly progressive renal involvement are characteristic of hydralazine associated vasculitis. Fatalities can occur in missed cases. In nearly all cases, patients test positive for p-ANCA and ANA in serum. Not uncommon is the presence of anti-ds-DNA, anti-histone, and anti-cardiolipin antibodies. HPE of ulcer site shows evidence of leukocytoclastic vasculitis and deposition of IgM, fibrin, and complement protein C3 in the

cutaneous blood vessels. Discontinuation of drug and symptomatic management form the mainstay of therapy. Steroids and immunomodulators such as cyclophosphamide may be required in some cases. Larger ulcers may need surgical debridement. Occurrence of vasculitis is an absolute contraindication of re-use of hydralazine [31, 32].

17.1.11 Levamisole

Levamisole is an anthelminthic and immunomodulator drug. The drug is used off label in nephrotic syndrome, gastrointestinal malignancies, and rheumatoid arthritis. Because of serious AEs like agranulocytosis, the drug was withdrawn from the USA. Having similarity with cocaine in taste and appearance and a euphoria supplementing action, the drug is mixed with cocaine unscrupulously. Following the use of levamisole adulterated cocaine, reports of vasculitis and cutaneous ulcerations have been reported in cocaine users. The entity is now named as cocaine-levamisole-induced vasculopathy syndrome (CLIVS). Lesions start as painful purpura on pinna, lower limbs, and upper limbs with gradual progression to full thickness skin lesions and ulcerations. HPE of lesions shows leukocytoclastic vasculitis and thrombosis of dermal blood vessels. Because of rarity of events, the exact pathogenesis needs to be delineated. Affected individuals show neutropenia and serum positivity for p-ANCA and c-ANCA. Urinary examination shows the presence of cocaine and levamisole. Treatment requires discontinuation of both offending drugs, symptomatic care and counselling. Corticosteroids may be required in systemic involvement [33].

17.1.12 Nicorandil

Nicorandil is used as adjuvant therapy in patients of stable angina. By opening the ATP sensitive K+ channels on vascular smooth muscles, the drug acts as a vasodilator and relieves the anginal pain. The common AEs include headache, hypotension, and tachycardia. It was in the late 1990s that the drug began to be associated with new onset mucosal ulcers in the oral cavity and perianal area. This was soon followed by reports of gastrointestinal ulcers involving the ileum, parastomal ulcers, and ulcers in the genital region. First case of pure cutaneous ulceration was reported with nicorandil in 2011 [34]. In a pharmacovigilance-based study of spontaneous reports of ulcerations with nicorandil, cutaneous involvement was seen in 27% of reported cases. In nearly 22% cases, the history of physical trauma or prior cutaneous lesions may be present. Cutaneous ulcers are generally seen in elderly patients, emerge after 2–4 years of therapy and commonly involve the lower limbs. Because of unawareness, often there is a delay of another 7–8 months in attributing the lesions to nicorandil [35]. In the absence of known predictors, a high index of suspicion should be kept at the very onset of ulcerative lesions and the drug should be stopped, and optimal wound care should be provided. Significant healing occurs

over next 2–3 months. Vascular steal phenomenon produced by the drug or accumulation of its toxic nicotinic acid metabolite in skin, are some of the mechanisms attributed to ulcer generation. Possibility of immune mediated reaction also exists.

17.1.13 Other Drugs

Tyrosine kinase inhibitors: Epidermal growth factor receptor (EGFR) inhibitors such as gefitinib and afatinib are known for their AEs on skin such as rashes and acneiform eruptions [36]. Multikinase inhibitors such as sunitinib, soratinib, nilotinib, and cabozantinib have been associated with hand and foot reaction and palmoplantar erythrodysesthesias [37]. Case reports of extremity ulcers including pyoderma gangrenosum exist with these inhibitors. Ulcers resolve following discontinuation of the culprit drug and symptomatic management [38–40].

Erythropoietin, Diltiazem, and Nifedipine: Case reports of cutaneous ulceration on lower limbs exist with recombinant erythropoietin (r EPO), diltiazem, and nifedipine [41–43]. Dermal vessel thrombosis leading to ulceration has been reported with r EPO in an elderly male with underlying small vessel disease, diabetes, hypertension, and renal insufficiency [41]. Nifedipine is known to cause dependant oedema in lower limbs that in rare cases can complicate to ulcers [42].

Cutaneous vasculitis and ulcers on lower limbs have been reported with diltiazem. However, patients being on multiple drugs, uncertainty exists with respect to association and mechanism of vasculitis with diltiazem [43].

17.2 Conclusion

Drugs constitute an important cause of new onset cutaneous ulcers. Direct toxicity on epidermal and dermal cells, vascular thrombosis, and vasculitis are the main mechanisms through which medications can produce ulcers over extremities. Ample evidence of extremity ulcers exists for drugs such as hydroxyurea, methotrexate, propylthiouracil, hydralazine, and anticoagulants. The pharmacologically characteristic ergotism is rare nowadays due to decline in the use of ergot compounds. Some drugs such as nicorandil have been characteristically linked with mucosal ulcers. The last decade, however, witnessed many reports of lower limb ulcers with nicorandil. With increase in the use of target-based therapy, evidence on cutaneous lesions and extremity ulcers is piling up for tyrosine kinase inhibitors. Since the field of pharmacologic evaluation is still underdeveloped in many countries, a significant delay occurs in attributing an ulcer developing in response to a drug. Timely involvement of a pharmacologist or performing an intensive drug review can expedite the diagnosis and prevent physical and psychological morbidity.

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