17 Differential Diagnosis: Vasculitis, Rheumatoid Arthritis, Behçet's Disease, and Thromboembolism

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Introduction

An ulcer is defined as the cutaneous loss of every part of the epidermis and at least the superficial layer of the dermis. In systemic sclerosis (SSc), digital ulcer (DU) can be simply defined as a digitally located loss of continuity in the epidermidis and adjacent layers, but sometimes, loss of ≥2 mm of palmar dermis reflects an ischemic etiology [1]. Although SSc is the predominant systemic DU etiology, other inflammatory and non-inflammatory conditions are associated with cutaneous and digital ischemia that affects the individual's quality of life and is a handicap. In this chapter, we review DUs and distal gangrene etiologies other than SSc, focusing more specifically on DUs associated with vasculitides and some inflammatory conditions, in which they are mostly the consequence of an ischemic process and often associated with gangrene.

Skin and Ischemic Manifestations of Systemic Necrotizing Vasculitis (SNV)

Cutaneous ischemia is a rare manifestation of SNV. In the retrospective study organized by the French Vasculitis Study Group, only 65 (5%) of the 1304 SNV patients had them [2]. DUs and digital necrosis (DN) are uncommon cutaneous manifestations of SNV [3]. The authors of three published series [3–5] of patients with cutaneous manifestations of granulomatosis with polyangiitis (Wegener's) (GPA) reported skin ulcers in 6–27% of them, rates which seem to be high. Notably, those series came from dermatology departments where DUs are more common, but the DU frequency in the general SNV population is probably lower. Ulcers were not located exclusively on the digits but also occurred in unusual sites, e.g., the perineal area [6], trunk, face, and neck [4, 5, 7]. Ulcers and other cutaneous ischemias can be the first manifestation of SNVs in 1–5% of patients [8].

Granulomatous manifestations associated with necrotic papules, like in GPA or eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA), must be differentiated from ulcers caused by ischemic necrotizing vasculitis located in small- or medium-sized skin vessels [3]. DN is a less frequent manifestation, mainly described in case reports that also emphasized the poor outcomes of DN in GPA, polyarteritis nodosa (PAN), and EGPA in adults [7, 9] and children [10, 11], with a higher amputation rate (67%) than in our personal series (25%) [2]. The condition affects mainly, but not exclusively, the fingertips. DN frequency is roughly the same in SNV. We observed digital ischemia in 7.1% of our MPA [12], 3.7% of our EGPA [13], and 6% of our PAN patients [14].

Cutaneous ischemia mechanisms in SNV are not fully understood. Causes may include necrotizing inflammatory obliteration of small-sized vessels, primary thrombus formation in a medium- or small-sized artery simultaneously affected with vasculitis, acquired thrombophilia, vasculitis-induced or

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preexisting endothelial dysfunction, and/or vasomotor disturbances. The case of a 12-year-old girl also suggested a role of vasospasm in digital ischemia and its reversibility with nifedipine [15]. Bessias et al. described multiple recurrent thromboses in femoral, popliteal, posterior tibial, anterior tibial, and peroneal arteries as signs of GPA onset that required a pregnant patient's below-the-knee amputation [16]. A patient with cryofibrinogenemia [10] and another with EGPA associated with antiphospholipid antibodies were also described [17].

Atherosclerosis plays a role, too. An association of subclinical atherosclerosis or artery dysfunction, e.g., SNV-induced endothelial dysfunction or arterial stiffness, was previously reported [18]. In addition, cutaneous ischemia has been associated with coronary atherosclerosis, smoking, and hypertension. Preexisting endothelial dysfunction secondary to well-known cardiovascular risk factors may worsen limb ischemia in SNVs. For DN, urging patients to stop smoking is still strongly warranted, even essential, in those SNVs. Inflammation, in turn, favors the atherosclerotic process, and its attenuation restores endothelial function [19].

DUs and digital ischemia are independent of the presence or absence of antineutrophil cytoplasmic antibodies (ANCA), as suggested by our results showing similar frequencies in patients with ANCA-associated vasculitides and PAN with or without vascular symptoms (Table 17.1) [2].

Table 17.1 Characteristics of systemic necrotizing vasculitis patients with or without cutaneous ischemia

Characteristic	With cutaneous ischemia (n = 65)	Without cutaneous ischemia (n = 1239)	P value
Age at diagnosis, mean ± SD years	54.6 ± 14.7	51.5 ± 17.0	0.23
First symptom to diagnosis, mean ± SD months	6.6 ± 8.0	7.1 ± 12.3	0.74
Diagnosis, n (%)			0.72
Microscopic polyangiitis	15 (23.1)	234 (18.9)	
Granulomatosis with polyangiitis (Wegener's)	18 (27.7)	372 (30)	
Polyarteritis nodosa	21 (32.3)	370 (29.9)	
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	11 (16.9)	263 (21.2)	
Cutaneous manifestations, n (%)	65 (100)	471 (38.0)	*<0.0001*
Nodules	8 (12.3)	134 (10.8)	*0.71*
Purpura	33 (50.8)	245 (19.8)	*<0.0001*
Livedo	13 (20)	98 (7.9)	*0.001*
Raynaud's phenomenon	11(16.9)	40 (3.2)	*<0.0001*
Associated factors, n (%)			
Gastrointestinal perforation(s)	4 (6.2)	22 (1.8)	*0.004*
Smoker (current or former)	22 (33.8)	282 (22.8)	*0.04*
Hypertension or smoking	33 (50.8)	419 (33.8)	*0.005*
Coronary artery disease	6 (9.2)	59 (4.8)	*0.04*

Data from Lega et al. [2]

Prognosis and Outcomes

Distal ischemic manifestations were not considered a poor-prognosis factor and were not items included in the 1996 and 2011 revisited five-factor score (FFS) [20, 21]. Although patients' outcomes did not differ according to the presence or absence of cutaneous involvement [3], that does not exclude the potential severity of these rare manifestations; it just means that they do not impact the final FFS. In our recent personal study, a link was found between cutaneous ischemia and poor long-term SNV outcomes [2]. DN was associated with an increased risk of gastrointestinal perforation, relapse with digital ischemia, other systemic manifestations, and vasculitis-related death. However, despite significantly increased frequencies of prior coronary artery disease, smoking, and arterial hypertension in patients with cutaneous ischemia, their survival rate did not indicate increased cardiovascular mortality.

Treatment

Because these clinical manifestations are severe and patients have poor outcomes, it seems reasonable to combine corticosteroids and an immunosuppressant or rituximab to treat patients with ANCA-associated vasculitides. When patients do not improve under this regimen, plasma exchange can be prescribed [22]. For limb ischemia caused by medium-to-large-sized artery disease, thrombectomy or bypass has been proposed [16, 23]. If either intervention is done, it should be combined with a general systemic regimen, as described above. Moreover, anticoagulation is recommended during the acute phase to treat and prevent thrombosis formation favored by endothelial injury and subsequent dysfunction. However, that recommendation has not been proven by prospective study or case series. Prostacyclin, mainly iloprost, can be added for ischemia but not for tissue necrosis, whose reversibility cannot be expected [11].

Rheumatoid Arthritis (RA)

DU is not a common RA feature; its presence characterizes rheumatoid vasculitis (RV). Even though RV is a rare phenomenon, whose frequency ranges from 15% to 31% of RA patients, some authors consider ischemic focal digital lesions a very common RV sign and a classical RA symptom [24]. RV occurs mainly in patient seropositive for rheumatoid factor and/or anti-cyclic citrullinated peptide. RV is considered to be an immune-complex disease. In addition, a relationship between it and three specific genotypes, **0401/*0401*, **0401/*0404*, and **0101/*0401*, of the *HLA-DRB1* shared epitope has been described [25] and a link with *HLA-C3* [26].

Histological examination usually shows small-sized vessel vasculitis, but in some patients, RV can affect medium-sized arteries and mimic PAN. Fibrinoid necrosis of the media and leukocytoclastic vasculitis are common, with disruption of the internal and external elastic laminae.

Clinical manifestations are ubiquitous and all organs can be affected. However, skin disease is one of the most common, with nail fold capillaritis, purpura, livedo, and, more rarely, nodules. Digital microinfarcts are frequently seen, usually subungual and visible through the nail, but they also can be periungual in the digital pulp. They are frequently associated with subcutaneous skin nodules. These microinfarcts are not considered factors of poor RV prognosis, unless they are associated with systemic manifestations. Some patients also have leg arterial ulcers that respond to vasculitis treatment. Livedo reticularis, purpura, and digital gangrene can occur, with the latter being considered to carry a poor prognosis. Among the other clinical manifestations, mononeuritis multiplex [27], poor general condition, and visceral involvements, e.g., gastrointestinal or cardiac manifestations, can be observed.

RV is diagnoses based on the skin, nerve, or muscle biopsy findings. RV incidence was estimated at 1–5% of RA patients, but its prevalence has dramatically decreased since more effective drugs, like methotrexate, antitumor necrosis factor (TNF), abatacept, and anti-CD20, have been widely used, with subsequent control of inflammation, which seems to be a major factor contributing to vascular injury. According to the recent analysis of the French Autoimmunity and Rituximab registry, 17/1994 RV patients have been described [28]; 82% of them responded to rituximab. However, it is too early to recommend this agent for systematic use in the RV therapeutic strategy. Voskuyl et al. reported the clinical characteristics of 31 patients with histologically proven RV: 4 had superficial skin ulcers, and 1 had gangrene. Among the 50 other patients with RA and extra-articular manifestations, 9 had superficial skin ulcers and 1 gangrene [29]. Still, arteriograms of three patients with leg ulcers and/or gangrene revealed occlusion of arteries, suggesting vessel disorders, even in the absence of RV [30]. One case report also advanced the possible implication of cryofibrinogenemia in DU pathogenesis in RV [31].

The RV prognosis was poor before the advent of "modern" therapeutic strategies. However, when this vasculitis occurs despite these treatments, outcome can be poor. A possible explanation could be RV-cause persistence because RA can remain active or at least persist in such patients. Only the RV form characterized by nail fold petechia has a good prognosis. For the other forms, including patients with digital ischemia, a combination of corticosteroids and cyclophosphamide (six to nine pulses, as described above), followed by azathioprine (2–3 mg/kg/day) or methotrexate (0.3 mg/kg/week) for 12 to 18 months, is recommended. Despite the

lack of controlled studies, anti-TNFα and rituximab have successfully treated RV. Mounting evidence suggests that TNF plays a central role in RV pathophysiology, and thus, anti-TNFα can be a therapeutic option [32]. Only case reports indicated efficacy of drugs commonly used to treat RA, e.g., methotrexate and anti-TNF (i.e., infliximab, adalimumab, etanercept) [30, 31]. The latter study provided evidence that anti-TNFα and corticosteroids achieved remission in six/nine patients with active refractory RV, thereby allowing notable corticosteroid sparing; however, the infection rate was high for those severely ill patients.

Although to date no argument supports the systematic prescription of plasma exchanges, they might be useful as second-line therapy for patients with severe RV and vascular gangrene or leg arterial ulcers who are rheumatoid factor- and cryoglobulinemia-positive.

Rituximab is also able to induce remissions: complete RV remission was obtained in most patients receiving rituximab, thereby enabling significant decreases of their daily prednisone doses along with an acceptable toxicity profile. In the French Autoimmunity and Rituximab registry [28], 12 (71%) of the 17 RV patients, among the 1994 RA patients entered, achieved complete vasculitis remissions after 6 months of rituximab administration, 4 had partial responses, and 1 died of uncontrolled vasculitis. The relapse rate was higher under methotrexate than rituximab, when one or the other was required as maintenance therapy for every patient. Notably, rituximab made it possible to lower corticosteroid doses. Some authors have also prescribed empirical rituximab successfully [33].

Behçet's Disease (BD)

BD is associated with bipolar aphthosis and thromboembolism. The International Study Group for Behçet's Disease described cutaneous lesions as a major criterion for the diagnosis [34]. Furthermore, BD comprises a wide variety of cutaneous lesions [35]. Hence, BD could be expected to be associated with DUs. To the best of our knowledge, only case reports on digital lesions of BD patients have been published. They mostly showed digital vasculitis with toe involvement [36], gangrene of the hand [37], or necrosis of the fifth foot digit [38]. Exceptional nodular lesions may also occur. Indeed, Cantini et al. described a unique case of a patient with recurrent, multiple, papulonodular, roundish, erythematous, painful, bluish-red nodules, 0.5–1 cm in diameter, on the palms and fingers of both hands [39].

Mucocutaneous Lesions of Behçet's Disease [35]

- Oral ulcers
- Genital ulcers
- Erythema nodosum-like
- Papulopustular
- Superficial thrombophlebitis
- Extragenital ulceration
- Pathergy reaction
- Cutaneous vasculitic
  - Sweet's syndrome
  - Pyoderma gangrenosum-like
  - Erythema multiforme-like
  - Palpable purpura
  - Subungual infarctions
  - Hemorrhagic bullae
  - Furuncles
  - Abscesses
  - Pernio-like
  - Polyarteritis-like
  - Acral purpuric papulonodular

However, hand involvement in BD is not that uncommon. A 2006 study reported BD patients' hand manifestations: among the 57 BD patients with specific hand examination, 32 had clinical findings, but no patient had DUs. Clinical hand involvement was associated with disease duration (OR = 3.4; $P < 0.05$). Pulp atrophy, observed in 17 patients, was the most frequent clinical finding [40].

Movasat et al. analyzed the nail fold capillaroscopies of 127 BD patients. Although findings were abnormal for 40% of them, no DUs were reported [41].

DU is a rare BD symptom and, unsurprisingly, caused by a vasculitic process. That process might be underestimated in the pathogenesis of skin lesions, as revealed by a histopathological study of 48 skin biopsy specimens from 42 BD patients [42]. In that study, 20 (48%) patients had cutaneous vasculitis, predominantly venulitis or phlebitis, with 17% leukocytoclastic vasculitis and 31% lymphocytic vasculitis. Clinical manifestations were mainly erythema nodosum-like eruptions, infiltrated erythema, and papulopustular lesions; only six patients had ulcerations.

No gold standard currently exists for BD treatment, and no randomized-controlled trial has examined reduction of vessel wall inflammation in BD [43]. Evidence-based recommendations concerning BD skin-mucosa involvement depend on the dominant or codominant lesions present [43]. Colchicine is widely used, because it was associated with

fewer mucocutaneous lesions, e.g., genital ulcers ($P = 0.004$) and erythema nodosum ($P = 0.004$) in women [44]. To treat leg ulcers, the European League Against Rheumatism task force advocated treatment selected according to the ulcer cause, which includes post-thrombotic, venous stasis, or vasculitic phenomena in BD, and highlighted the lack of controlled evidence for vascular involvement. Treatment of resistant cutaneous lesions relies on azathioprine, thalidomide, interferon-α, and/or TNFα antagonists [43].

Alibaz-Oner et al. recently investigated the therapeutic approach to vascular BD in Turkey based on their retrospective study on 936 patients: 363 (38.7%) had mucocutaneous disease, and 260 (27.7%) had vascular involvement [45], with the latter being the first sign of the disease for 149 (57.3%). Notably, vascular involvement was not held responsible for any mucocutaneous lesions. Vascular BD was treated with immunosuppressants (e.g., corticosteroids, methotrexate, azathioprine, cyclophosphamide, infliximab, or interferon-α) and an anticoagulant, like warfarin and conventional or low-molecular-weight heparin. Immunosuppressants, given to 88.8% after the first vascular event, were negatively correlated with vascular manifestation relapse. Adjunction of an anticoagulant to an immunosuppressant was not associated with a positive effect on vascular relapse.

Overall, DUs in BD are rare and mainly associated with vascular involvement of the disease, which is mostly treated with immunosuppressants, despite the lack of consensus.

DU-Associated Thrombosis

Antiphospholipid Syndrome

Although SSc is a main cause of DUs, the latter could be masking something else, and antiphospholipid syndrome (APS) can also be associated with DUs in this setting. Indeed, Küçükşahin et al. described a patient with limited cutaneous SSc complicated by treatment-resistant digital ischemia [46]. The lack of response to conventional therapy led to biological analyses and proof of APS; warfarin was added and the digital lesion regressed.

Digital manifestations of APS include acute ischemia and gangrene [47–49]. In a European cohort of 1000 APS patients, the estimated frequency of leg ulcers, pseudovasculitic lesions, and digital gangrene, respectively, was 5.5%, 3.9%, and 3.3% [50]. At disease onset, 1.9% of the patients had digital gangrene [50]. A few years later, Francès et al. reported the dermatological characteristics and symptoms of 200 APS patients. Among the 15 (7.5%) APS patients with DN, it was the presenting sign for 5 [51]. Digital lesions can occur at any age [52–54], at any time during APS evolution, and are rarely an isolated symptom [55]. They occur in primary and secondary APS, such as systemic lupus erythematous (SLE)-associated APS [56]. Nail fold capillaroscopy can be a useful tool in APS to detect microscopic abnormalities, mainly hemorrhages, edema, or bushy capillaries [57], or suggest differences between primary APS- and SLE-associated APS by showing more microhemorrhages in the latter than the former [58].

Possible pathogenic mechanisms include an ischemic process, due to fibrin microthrombi forming in the vessels [59], and a vasculitic process [60]. In the series reported by Francès et al., digital gangrene was related to medium- or large-sized vessel occlusion [51].

Notably, digital ischemia and APS can reveal anecdotal situations, for example, familial APS [61] or malignancy-associated APS and metastatic colon cancer or poorly differentiated metastatic epithelial carcinoma [53]. Intriguingly, in their retrospective study on 21 APS patients of different national origins who endured limb or digit amputation, Asherson et al. emphasized that livedo reticularis appeared before arterial thrombosis in 9 of them [60].

Digital manifestations of APS must be treated with anticoagulation, the essential cornerstone of its therapy. Moreover, digital gangrene is a severe manifestation of the disease that requires acute anticoagulation with heparin and then long-term warfarin [51]. Iloprost and plasma exchange have also been reported to be effective, when heparin failed to impact skin lesions [51, 62, 63]. Oral non-vitamin K antagonist anticoagulants are currently being evaluated for APS [64].

Thromboangiitis Obliterans (TAO)

TAO, also known as Buerger's disease, is a non-atherosclerotic segmental inflammatory disease of small- and medium-sized arteries of the distal extremities of predominantly young male smokers. The diagnosis, mainly clinical, is suspected when ischemic lesions of the distal limbs are present [65]. Common onset symptoms include gangrene, acral ulcer, ischemic rest pain, subungual and/or skin infection(s), phlegmon(s), claudication, acral skin discoloration and coldness, Raynaud's phenomenon (RP), and thrombophlebitic nodules [66]. TAO ulcers are distal and associated with clubbing, pain, and bluish discoloration of the fingers when exposed to cold [67, 68].

Quitting smoking is a mandatory treatment measure, as it favors ulcer healing and can prevent new ulcer formation and/or amputation [69]. Intravenous iloprost for 28 days effectively heals ulcers and relieves TAO-related pain. In the

first randomized, double-blind trial comparing iloprost to aspirin that enrolled 152 TAO patients, Fiessinger et al. showed that 85% of the iloprost-treated patients reached the primary endpoint (ulcer healing or relief of ischemic pain) compared to 17% of those given aspirin [70]. In 2013, Bozkurt et al. confirmed those results in 60% of 158 patients treated with intravenous iloprost for 28 days [71]. Other TAO treatments include antiplatelet agents, anticoagulants, and vasodilating drugs, but there is no evidence of their efficacy [66]. At present, no proven indication supports sympathectomy or immunosuppressive agents for TAO [66]. As for SSc, bosentan has been evaluated for TAO. A pilot study assessed the reoccurrence of ischemic lesions in 12 TAO patients (13 extremities) treated with bosentan in a compassionate use program [72]. In that evaluation, which unfortunately lacked a control group, 11 patients had toe or finger ulcer(s) at study onset. At the end of the study, only 1 patient had developed new ischemic lesions, and 2 of the 13 extremities were amputated. Bosentan for TAO is not currently under evaluation in ant phase III clinical trial (www.clinicaltrial.gov).

Vascular Embolism

Because embolic disease is a well-recognized cause of acute digital ischemia, every potential embolism etiology should be considered when managing a patient with digital ischemia, especially when the patient has a pulseless, unilateral acute lesion. Arterial stenosis or aneurysm can cause acral emboli, which clinically give rise to a blue finger syndrome, which requires endovascular intervention [73]. Aneurysms of ulnar [74], axillary or subclavian arteries, and other thrombotic conditions, e.g., a descending thoracic aorta mass [75] or arteriovenous fistula [76], have been reported. Other etiologies of digital embolic lesions include cholesterol embolism [77], bacterial septic embolism [78], atrial fibrillation, myxoma, and intracardiac thrombosis [79].

Conditions favoring a procoagulant state, such as thrombocythemias, thrombophilia, paraproteinemia, and cancer, should also be sought for the differential diagnosis of digital embolic lesions [80].

Vascular Spasms

Raynaud's Phenomenon

Maurice Raynaud first characterized RP in 1862. Its hallmark is ischemia of the digits in response to cold. RP is diagnosed clinically. It is then subclassified into primary or secondary RP. Primary RP diagnostic criteria include those for RP and exclusion of secondary causes, as assessed by a capillaroscopy, physical examination, history of connective tissue disease, and antinuclear antibody serology [81]. Secondary RP causes include vasoconstrictive medication, autoimmune disorders (SSc, mixed connective tissue disease, RA, SLE, dermatomyositis, Sjögren's syndrome), vasculitis, arteriopathies, dysthyroidea, acromegalia, malignancies, and professional wrist trauma [82]. Primary RP is usually not associated with DUs, but exceptional fingertip necrosis has been reported [83, 84]. In Landry et al.'s longitudinal study, 7.7% of 585 patients with vasospastic RP had DUs at their initial evaluations, and 14% of 50 patients had them after 10 years of follow-up. Nine (1.5%) patients initially and only two (4%) after 10-year follow-up underwent digital or phalangeal amputation [85].

RP treatment includes patient education, warmth maintenance, cold avoidance, and various pharmacological therapies, among which, calcium channel blockers are widely prescribed [86].

Ergotism

Ergot alkaloids are metabolites of fungus species of the genus *Claviceps*, most commonly *Claviceps purpurea*. The *Claviceps* fungus and, thus, ergotism might have been responsible for one of the plagues of Egypt, as it could have contaminated grain and storage facilities opened by the oldest sons just before dying of arterial ischemia [87]. Ergotism is also called Saint Anthony's fire, which refers to the intense inflammation caused by eating food prepared with ergot-contaminated rye during the Middle Ages [88].

Nowadays, ergotism is a rare etiology of arterial ischemia that is mainly seen in human immunodeficiency virus-infected patients [89] and/or those treated with ergot alkaloids for migraine [90]. It is mainly due to drug interactions or overexposure to ergot derivatives, e.g., ritonavir or ergotamine [91]. It affects the extremities, causing leg ischemia, ulcers, and gangrene as common manifestations [92]. Treatment requires the discontinuation of all ergot-containing medications, cessation of caffeine intake, and stopping smoking. The prognosis can be poor as for a reported limb amputation [93], but iloprost has also been used effectively [92, 94].

Iatrogenic Spasm

Medications other than ergot-containing drugs can be responsible for vascular spasms, for example, high-dose epinephrine, *coxibs* (e.g., COX-2-selective nonsteroidal anti-inflammatory drugs) [95], and nonsteroidal anti-inflammatory drugs like diclofenac [96], nabumetone [97], and naproxen [98].

Other Causes

Other possible DU causes (e.g., congenital, tunnel syndrome, frostbite, local trauma, drugs or mercury injections, psychological parasitophobia, infections) that should also be considered in the differential diagnosis of DUs are summarized below, which concludes this overview of the differential diagnoses of DU.

Other Uncommon Causes of Digital Ulcers

Congenital
- Porphyria [99]
- Aicardi-Goutières syndrome [100]
- Familial chilblain lupus [101]

Mechanical
- Carpal tunnel syndrome [102]
- Local microtrauma
- Self-injections (drugs, mercury) [103, 104]

Frostbite [105]

Infectious
- Bacteria: purpura fulminans [106], *Bacillus anthracis*, *Neisseria gonorrhoeae*, *Treponema pallidum*, pyogenic granuloma, bacillary angiomatosis [107]
- Mycobacteria: tuberculosis, atypical mycobacteria, leprosy
- Viruses: human immunodeficiency virus, herpes simplex virus, human herpesvirus-8, *Parapoxvirus*, orf virus
- Fungi: sporotrichosis [108]
- Parasites: leishmaniasis [109], trypanosomiasis

Malignancies and Kaposi's syndrome [110–115]

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