SMGroup

Skin in HIV

Title: Skin in HIV

Editor: Leelavathy Budamakuntla

Published by SM Online Publishers LLC

ISBN: 978-0-9962745-2-4

First published April, 2015

Online Edition available at http://www.smgebooks.com

For reprints, please contact us at ebooks@esciencemedicine.com

Vascular Diseases in HIV

Shwetha S and Aparna D

Department of Dermatology, STD and Leprosy, Bangalore Medical College and Research Institute, India.

***Corresponding author:** Leelavathy B, Department of Dermatology, STD and Leprosy, Bowring and Lady Curzon Hospital, Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India, Email: drleelaskincare@rediffmail.com

Published Date: April 15, 2015

HIV has brought an array of new clinical presentations and has also generated new syndromes [1]. HIV vasculopathy was first described as an entity in 1987 [2] and may present with arterial occlusive disease and aneurysmal disease, or spontaneous arteriovenous fistula [3-6]. The incidence of symptomatic vasculitis is in the region of 1% of HIV-infected patients [7].

VASCULITIS

INTRODUCTION

The manifestations of human immunodeficiency virus (HIV) infection are protean and vasculitides are one of the less common but nonetheless important consequences. A wide range of vasculitides have been encountered, ranging from vasculitis resulting from specific infective agents to a non-specific vasculitis.

TYPES OF VASCULITIS SEEN IN HIV

Calabrese has divided the vasculitides associated with HIV infection into four major categories: polyarteritis nodosa like illness (PAN) and other systemic necrotizing vasculitides, hypersensitivity vasculitis, lymphomatoid granulomatosis and primary angiitis of the CNS [8]. Almost every pattern

and type of vasculitis of small, medium and large vessels has been described in the HIV setting. An important caveat to the understanding of the relation between vasculitis and HIV involves epidemiological, clinical, and pathophysiological considerations [8]. From an epidemiological point of view, it is not clear whether HIV and vasculitis are causally or coincidentally related. Clinically, other presenting conditions related to different systems and organs may well mask the vasculitis. In terms of pathophysiology, the concurrence of other pathogens, in particular viruses such as EBV, HBV, and CMV, which are all associated with vasculitis, complicates the issue. Thus, it can be concluded that HIV associated vasculitis might be associated with a known pathogen or triggering factor, or may occur in the absence of an obviously identifiable agent or aetiopathogenesis [9]. This means that almost all causes of vasculitis can be seen in HIV positive patients. Given this background, it is not surprising that the literature abounds with case reports and series of the various entities associated with vasculitis. Most of these examples have been categorised according to well known and recognised vasculitides that are also seen in patients without HIV infection. An extremely diverse array of vasculitides is encountered but it must be borne in mind that the real incidence of vasculitis in HIV positive patients is low and in the order of 1% [7].

INFECTIVE VASCULITIDES

Opportunistic infections are common in patients with HIV infection and vasculitis may be a manifestation of this infection. Infectious agents of all types and classes can cause vasculitis of arteries and veins of all sizes and in all organs [9,10]. CMV, HZV, toxoplasmosis, pneumocystis, salmonella, and *Mycobacterium tuberculosis* have all been associated with vasculitis in patients with HIV infection [11]. The diagnosis is dependent on one or more diagnostic modalities including serology, culture, light microscopy, immunohistochemistry, and in situ hybridization [9]. There are cases of vasculitis in HIV positive patients in which a causative agent is not found despite the use of the above mentioned techniques. It is this residue of cases of vasculitis that can be regarded as the result of direct infection by HIV [12]. Infected false aneurysms of large vessels have been described in HIV positive drug addicts, especially in large arteries such as the femoral artery (Figure 8.1).

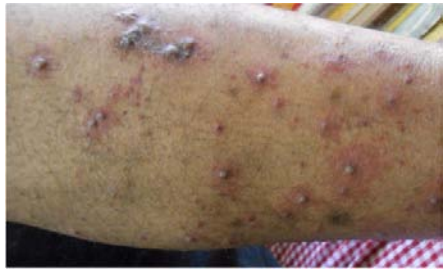

Figure 8.1: Infective vasculitides secondary to Cryptococcosis.

(Photocourtesy: Bowring and Lady Curzon Hospital, Bangalore)

Two theories have been proposed to explain the virus associated vasculitis [8]. The virus may attack the vessel wall directly or cellular or humoral immune mechanisms involved in the disease may lead to the formation of in situ or deposition of circulating immune complexes that subsequently result in the development of vasculitis. The demonstration of vascular deposits of HIV antigens, immunoglobulins and compliment components suggests an immune / or complement deposition process. It is also suggested that in patients with HIV disease, the pathogenesis is multifactorial and may result from HIV induced immunologic abnormalities and response to a variety of xenoantigens including HIV, other opportunistic infectious agents and drugs used for the treatment [13].

POLYARTERITIS NODOSA-LIKE SYNDROME AND OTHER SYSTEMIC NECROTISING VASCULITIDES

The PAN like illness presents most commonly as peripheral neuropathy or as ischaemic changes in the limbs. In contrast to the high prevalence of renal involvement in idiopathic PAN, none of the reported cases associated with HIV infection have significant renal disease. The target organs that are usually involved are muscles and nerves, although skin and the gastrointestinal tract can also be involved [8].

In general, there are two modes of presentation:

A) Peripheral neuropathy

B) With digital ischaemia.

The clinical spectrum of the neuropathy ranges from mononeuritis multiplex and symmetrical sensorimotor polyneuropathy, to distal sensory neuropathy and ascending myeloradiculopathy [14].

The neurological deficit develops either insidiously or rapidly over a period of weeks. General constitutional symptoms such as fever, malaise, and weight loss are also encountered and are related to the vasculitic process.

There are several important differences between PAN seen in the HIV setting and so called classic or idiopathic PAN [14].

A) First, the waxing and waning clinical course of classic PAN is not seen in patients with HIV infection.

B) Second, it is well recognised that classic PAN can be associated with viral infections, especially HBV, but in HIV associated cases serology for HBV is invariably negative [8,14].

C) Third, multisystem organ involvement, particularly renal involvement, is not seen in HIV associated cases.

D) Lastly, Gherardi and colleagues observed that the affected arteries in HIV associated PAN tend to be smaller than that seen in classic PAN [18].

HYPERSENSITIVITY VASCULITIS

Within the rubric of hypersensitivity vasculitis, are several vasculitides that manifest in the skin and display a small vessel involvement with leucocytoclasia. Palpable purpura and sometimes neurological deficit are usual modes of presentation. Henoch-Schonlein purpura(HSP), drug induced hypersensitivity vasculitis, and cryoglobulinaemia have all been encountered in the HIV setting [8,14,15] (Figure 8.2 and 8.3). Hypersensitivity vasculitis is also seen with other viruses such as CMV,EBV, and HBV in patients with HIV [17,18,19]. Because these viruses can cause a vasculitis without coexistent HIV infection, it is best to regard the vasculitis in the presence of these other viruses as the result of the virus and not of HIV infection. In those cases without identifiable viruses, then hypersensitivity induced by HIV is deemed causative [9].

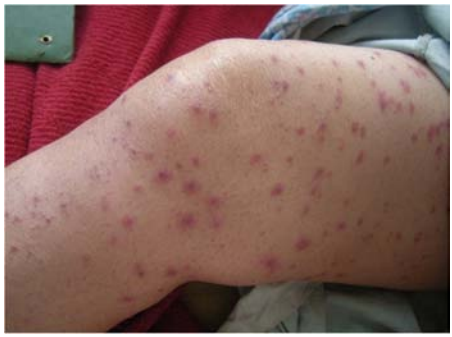

Figure 8.2: HS purpura: Palpable purpura over lower limb in HIV positive female with Hepatitis B infection.

(Photo courtesy: Department of Dermatology, Bowring and Lady Curzon Hospital)

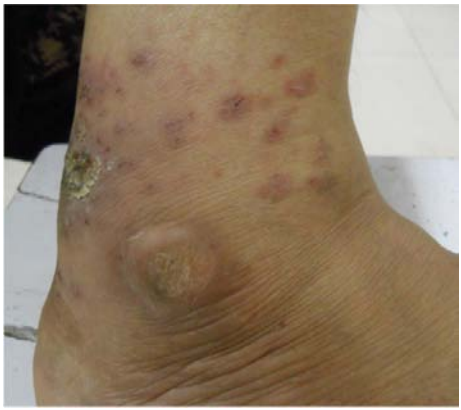

Figure 8.3: Small vessel vasculitis in HIV positive patient.

(Photo courtesy: Department of Dermatology, Bowring and Lady Curzon Hospital)

LYMPHOMATOID GRANULOMATOSIS AND ANGIOCENTRIC IMMUNOPROLIFERATIVE LESIONS

Angiocentric immunoproliferative lesion is probably the preferred term because within this broad definition both benign and malignant proliferations are included. There are several reports of these lesions in patients with HIV infection ranging from lymphomas to benign lymphocytic angiitis of T cell lineage [8]. The mechanism that has been suggested is based on HIV induced immune dysregulation leading to proliferation of T cells with an angiocentric proclivity [9].

PRIMARY ANGIITIS OF THE CENTRAL NERVOUS SYSTEM

This is a rare condition associated with a high mortality [8]. It is characterised by a granulomatous inflammatory infiltrate, often with multinucleated giant cells. It is, of course, mandatory to exclude tuberculosis in this setting. Any part of the central nervous system can be affected but small arteries and veins on the brain surface and associated with the leptomeninges are usually involved. Primary angiitis of the central nervous system is not specific to HIV and can be seen when the immune system is compromised for any reason.

The association between HIV infection and stroke is slightly controversial. Some authors have suggested that the increased risk of stroke, in particular cerebral infarction in young patients, is related to HIV infection, susceptibility to meningitis, and protein-S deficiency [20]. However, a case controlled study found that the rate of stroke in HIV positive patients was no higher than that seen in seronegative patients [21]. This study did demonstrate that the incidence of large vessel cryptogenic stroke in HIV positive patients suggested a prothrombotic state. One of the effects of cerebral vasculitis as a result of HIV infection is a putative opening up of the blood–brain barrier. This can lead to HIV infected and uninfected cells passing into the central nervous system, resulting in HIV encephalitis [22].

Aetiopathogenesis

The exact mechanisms by which the vasculitic processes described above occur in the HIV

setting are still somewhat conjectural.

1. The most obvious ones are the infective vasculitides. Although the vasculitides encountered in the HIV positive patient are highly heterogenous, they are underpinned by a common histopathological tenet: inflammation of the vessel wall. This basic pathological process is probably multifactorial [9].

2. Mandell and Calabrese have speculated on the pathogenesis of HIV vasculopathy. These patients, being immunocompromised, frequently have other infections or cofactors that might be responsible for the vasculitis. Clearly, there is a large number of cases where no obvious aetiological agent is apparent. In these cases, an indirect effect of HIV infection via an immune complex mediated mechanism or a direct infection of vascular or perivascular tissue has also been

suggested [23]. In fact, Gherardi and colleagues identified HIV particles by electron microscopy and in situ hybridization in the perivascular tissues of patients with PAN-like vasculitides. Although not conclusive, this is circumstantial evidence pointing towards HIV being the causative agent.

3. The lymphocytes seen in the adventitia and periadventitial tissue are almost exclusively of the T cell lineage. T cell mediated vascular injury has been demonstrated in several vasculitides including PAN, Takayasu's and Wegener's arteritis, and leucocytoclastic vasculitis [24]. It is known that in HIV there is an oligoclonal expansion of T cells, especially CD8 positive cells. An interaction of these lymphocytes (which might release growth factors), superantigens, adhesion molecules, immune complexes, cytokines, and growth factors is likely [9].

LARGE VESSEL VASCULOPATHY

Aneurysms

This disease affects much younger patients than those with degenerative atherosclerotic aneurysmal disease. The median age is between 30 and 40 years [25-27]. However, the majority of patients infected with HIV are females and the reason for the male preponderance of aneurysmal disease is unknown [26,27].

Pathogenesis

The pathogenesis of the aneurysms is uncertain. Histology shows obliterative endarteritis involving the vasa vasora of the major vessels. These vessels are surrounded by neutrophils, which in turn are surrounded by a cuff of plasma cells, lymphocytes and monocytes. This eventually leads to thrombotic occlusion of the vasa vasora with transmural necrosis of the vessel wall, probably due to ischaemia. HIV protein is noted in the lymphocytes, but the significance of this is uncertain as this is noted in lymphocytes throughout the body of HIV infected patients [25].

Routine cultures of the aneurysm wall have revealed no bacteria or other opportunistic infection, but this has been noted in one or two cases and is thought to be a sporadic finding. The pathogenesis is possibly related to some immune complex mechanism [28].

Sites of aneurysms

The common sites for the aneurysms are the common carotid and the superficial femoral artery. They can, however, be found throughout the body, tend to be multiple, and typically have a multi-loculated appearance. Many are in fact false aneurysms due to disruption of the vessel wall at the point of transmural necrosis [25,26].

Clinical features

Symptoms and signs depend on location of the aneurysm and, for example, there may be compressive symptoms due to airway obstruction or possibly haemodynamic instability due to rupture. Thromboembolic complications are also frequent, as is associated venous thrombosis.

Any patient presenting with aneurysm should be screened for multiplicity using ultrasound and CT scanning as required [28].

Management

Management of the aneurysms is according to their respective merits and patients with symptomatic lesions should not be denied therapy. However, judgment can be tested in severely malnourished and ill patients with asymptomatic lesions. The standard therapy involves open surgery following standard principles. Endovascular therapy is increasingly being applied and is an attractive option in these ill patients. Patients should be optimized as per standard practice prior to intervention although those with full-blown AIDS are probably best managed conservatively. The combination of a low CD4 count and low albumin (less than 35 g/l) are pointers towards poor operative results [29,30].

Conclusion

Vasculitis in an HIV positive patient is an uncommon but important disease that might manifest as an organ based disease process. Many types of vasculitis have been reported, mainly of small and medium sized vessels. Large vessels can also be involved; usually as part of a leucocytoclastic vasculitis of the vasa vasora or periadventitial vessels. An infective aetiology should always be sought so that appropriate treatment can be instituted [11].

HIV ASSOCIATED VENOUS THROMBOEMBOLISM

HIV infection has been recognized as a prothrombotic condition and this association has now been proven by a large number of studies. In fact many epidemiological studies reported on the occurrence of VTE among HIV-infected patients with a frequency ranging from 0.19 to 7,63 %/year [31-42]. Of interest recently Rasmussen found that the 5-year risk of VTE was 8.0% in injecting drug users (IDU) HIV-infected patients, 1.5% in non-IDU HIV-infected patients and 0.3 % in the population comparison cohort [43].

Mechanism

Although HIV-infected patients are at increased risk for venous thromboembolism little work has been done on defining the exact mechanisms by which this phenomenon occurs, and still less has been done on evaluating the role of thromboprophylaxis in HIV-infected individuals [44].

Risk Factors for Thromboembolism in HIV-Infected Patients

VTE is a multicausal disease and most commonly is the result of more than one “Hit”. The probability of developing venous thromboses would depend on type and number of risk factors involved. Many established factors are known to increase the risk of VTE in general population [45]. Furthermore several specific factors are thought to be associated with VTE in patients with HIV[44].

Host Risk Factors

Age

The incidence of venous thromboembolism increase dramatically as the population ages, from 0.001% a year in childhood to nearly 1% a year in the elderly [46]. The incidence of venous thromboembolism increase dramatically as the population ages, from 0.001% a year in childhood to nearly 1% a year in the elderly [46]. Because most HIV infected people are relatively young, their risk of DVT should be expected to be lower than the overall incidence. HIV-infected patient are in fact older than their chronological age and they experience the so-called "Premature Aging". In this immunological ageing the immune system has persistent defects even after years of treatment mediated viral suppression. The heightened risk for premature aging is also the result of residual immunodeficiency and inflammation [44,47].

Intravenous drug use

Rasmussen first show the impact of intravenous drug use on risk Of VTE in HIV-infected patients [43]. This study found that the risk of VTE was nearly 15 times higher in IDU HIV-infected patients that in non IDU HIV-infected patients [44].

Hypercoagulable state

a) **Protein S deficiency:** Protein S deficiency is the most consistently observed coagulation abnormality observed in HIV-infected patients. Type III protein s deficiency is the most common abnormality found and characterized by a normal total protein S level with a decrease in both free protein S and functional protein S activity [48]. Decreased synthesis by the endothelial cells, hepatocytes and megakaryocytes injured in HIV infection has been proposed [44,49] tumor necrosis-factor-alpha (TNF-α) can lower the levels of active protein S down-regulating the protein S synthesis in the endothelial cells [50]. Another publication showed how the occurrence of PS deficiency might be linked to the presence of antiphospolipid antibodies [51].

b) **Protein C deficiency:** The mechanism of protein c deficiency in HIV infected persons is multi-factorial, including altered synthesis and metabolism as well as low-grade disseminated intravascular coagulation (DIC) with consumptive coagulopathy [52].

c) **Antithrombin deficiency:** Acquired AT deficiency frequently occurs in the course of HIV disease as a consequence of associated conditions that cause decreased protein synthesis (liver diseases eg HCV coinfections and malnutrition), protein-losing nephropathies or enteropathies, consumptive states (malignancy, DIC, surgery)**.**

d) **Antiphospholipid and lupus anticoagulant antibodies:** The frequency of Antiphospholipid anytibody syndrome(APS) in the general population is 2–4%, and is clearly linked to increased risk of venous and arterial thrombosis [53]. Anticardiolipin antibodies have been reported in HIV-infected patients with a prevalence ranging from 7% to 94% [54]. Actually

is thought that lupus antibody activity in those patients might be an epiphenomenon secondary to chronic immune stimulation in HIV infection [44].

e) **Tissue Factor:** Funderburg et al [55] found dramatically higher frequencies of monocytes expressing tissue factor (TF) in fresh blood samples from HIV-infected persons than in samples from uninfected controls. They postulated that a variety of bacterial toll-like receptor (TLR) ligands, such as peptidoglycans, lipopolysaccharide (LPS), and flagellins, are translocated through the damaged gut in chronic HIV infection and may drive immune activation (in addition to HIV viral Replication) and monocyte TF expression in this setting [44,56]. HIV replication and systemic translocation of microbial products from the damaged gut, and the subsequent immune activation, contribute to a procoagulant state in HIV-infected patients that is due, at least in part, to increased surface expression of TF on circulating monocytes [56,57].

f) **Microparticles:** The term "microparticles" (MP) refers to a small (< 1mμ) membrane vesicles released from activated or apoptotic cells [58]. The MPs may be generated from, vascular smooth muscle cells, endothelial cells, platelets, apoptotic CD4+ lymphocytes and from tumor cells [59]. It is found that these microparticles are increase in HIV patients compared to non HIV patients. These microparticles might cause VTE.

g) **Homocysteine:** Mild to moderate Hyperhomocysteinemia (HHcy) is relatively common in HIV-infected individuals (prevalence ranging from 11 to 29%) [60,61]. HHcy may add an additional risk among patients with other risk factors for venous clots.

h) **Endothelial Dysfunction:** Many studies showed a strong association between endothelial cells abnormalities and VTE in general population [62-64]. Under normal conditions endothelial cells exert a vasodilatory, antiplatelet and local fibrinolytic tone that prevents platelet adhesion, leukocyte attachment, as well as blood coagulation [44]. In the context of VTE, a dysfunctional venous endothelium may express increased amounts of P-selectin, von Willebrand factor (vWF), tissue factor (TF), plasminogen activator inhibitor-1 (PAI-1), and factor V, all of which may promote blood clotting and participate in the development of a thrombus [44,65]. It is now well established that the endothelium could be activated directly by HIV virus. In fact multiple studies reported the role of HIV in causing endothelial dysfunction [66,67].

Viral risk factors

a. **CD4+ Cell Count:** The severity of the HIV infection appears to be of significance in association with VTE. In fact several studies confirmed that there is a higher incidence of venous thrombosis in patients with low CD4 counts [52,68-70]. Although the frequency of VTE is higher in the presence of lower $CD4^+$ cell counts, there are reports of thrombosis occurring with $CD4^+$ cell counts as high as 800 cells/mm^3, suggesting that the risk of thrombosis is not completely confined to patients with end-stage disease [42]. The correlation between CD4 count and the risk for the development of thromboses may be related to an increasing hypercoagulable state found with progressive immune suppression and HIV disease progression.

b. **Viral Load:** Another indicator of high disease burden of HIV infection is viral load, also known as HIV RNA level. Low $CD4^+$ cell counts and high viral loads are predictive of progression of HIV and typically complement each other in the absence of treatment [44].

c. **Opportunistic infection:** In spite of the efficacy of HAART, HIV-positive individuals are at the greatest risk for developing opportunist infections depending to their immunologic status. So the concomitant presence of advanced HIV disease and opportunistic infections appears to be an additional risk factor for Thrombosis [8,13,14,44,71,76]. VTE is most commonly reported with Cytomegalovirus and *Pneumocystis jiroveci* pneumonia (PCP) and Mycobacterium avium-intracellulare [72] *Mycobacterium tuberculosis* is able to activate macrophages directly and induces them to produce cytokines, especially TNF-α, IL-1 and IL-6. TNF-α and IL-1 blocks the protein C anticoagulant pathway and can elicit tissue factor production on endothelium and monocytes [73]. IL-6 can also stimulate new platelets formation which have increased sensitivity to thrombin activation and increased pro-coagulant activity. The prevalence of VTE in Tuberculosis patients is ranging from 0.6% to 3%, while the prevalence of VTE in patients with coexisting HIV and tuberculosis is unknown [44,74,75].

HIV-associated malignancy

The risk of VTE in patients with cancer varies considerably between patients and even within an individual patient over time. Estimates ranging from 15 to 30 % have been reported [76]. It is well-known how patients with no identifiable risk factors who develop DVT may have an underlying occult malignancy [77]. People with HIV infection and AIDS have an elevated cancer risk [78]. Compared with the general population, HIV-infected individuals have a 3640-fold increased risk of Kaposi sarcoma (KS), a 77-fold increased risk of non-Hodgkin lymphomas (NHL), and a six-fold increased risk of cervical cancer [79,80]. These malignancies are AIDS-defining cancers, based on the Centers for Disease Control and Prevention (CDC) definition of AIDS [81]. HIV-infected people also have an increased risk of a number of non-AIDS-defining cancers, including some associated with co-infections (eg, anal and oropharyngeal cancers associated with HPV infection, liver cancer associated with infection with hepatitis B and C viruses, and Hodgkin lymphoma associated with Epstein–Barr virus infection [44,80]. Kaposi Sarcoma (KS) is the most common malignancy reported in literature associated with VTE in HIV-patients. Several reviews regarding thromboembolism in patients with KS in HIV-infected patients have reported an incidence of thrombosis ranging from 9.3% to 20% [36,42,44,82]. The remaining malignancies were reported as single cases of primary CNS Lymphoma, B-cell non-Hodgkin lymphoma, Hodgkin disease, prostate cancer, anal cancer, colon cancer [36,42,44].

Drug risk factors

a. **HAART:** Protease inhibitors can cause thrombotic events in HIV patients. PI are thought to interfere with hepatic metabolism, specifically cytochrome P450 metabolism, and regulation of thrombotic proteins. This may ultimately cause a prothrombotic state in HIV-infected individuals

and therefore increase the risk of a thrombotic episode. Otherwise they may either downregulate the anticoagulant effect within the body or generate endothelial or platelet dysfunction [37]. However, the risk arises when there is concurrent risk factor associations [44].

b. **Megestrol:** Megestrol acetate is a synthetic, orally active, progestational agent, used widely in the treatment of metastasic breast cancer. It has also been reported to stimulate appetite and weight gain in patients with AIDS-related anorexia and/or cachexia. In these groups of patients thromboembolic phenomena as adverse events potentially related to megestrol have been reported [44,83,84].

Management

The 2008 ACCP guidelines on antithrombotic and thrombolytic therapy do not mention HIV-infected patients. Nevertheless clinicians dealing with HIV must be aware that this high risk population needs particular attentions regarding antithrombotic prophylaxis and therapy looking at them in the same way as it would be for patients suffering from cancer. The management of proven VTE in HIV-infected patients should be the same as for the non HIV-patients, including long-term prophylaxis with low molecular weight heparin and warfarin for patients with recurrent thrombosis [44].

Antiretroviral Therapy and Warfarin Drug Interaction

Because of an increased risk of thromboembolism in patients with HIV/AIDS and the increasing longevity of the HIV-infected population receiving effective antiretroviral therapy, more HIV-positive patients will be receiving in the future concomitant oral anticoagulant and antiretroviral therapy [44].

Interactions between warfarin and antiretrovirals is possible, given the influence of many antiretrovirals on CYP2C9 the enzyme responsible for the metabolism of the more active S-enantiomer of warfarin [44,85].

Among the antiretrovirals, interactions involving non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) with warfarin are most likely to occur. Inhibition or induction of metabolism requiring warfarin dosage adjustment may be observed, depending on the specific antiretroviral drug. Among the NNRTIs, induction of warfarin metabolism is likely with nevirapine. Inhibition of warfarin metabolism may occur with efavirenz, delavirdine, or etravirine, but more evidence is needed to characterize the nature and onset of these interactions. Interactions involving ritonavir-boosted PIs are most frequent when warfarin is initiated in patients receiving concurrent efavirenz therapy. It seems prudent to base warfarin dosage adjustments on International Normalized Ratio (INR) response rather than empirically beginning with a lower warfarin dose. Perhaps alternative forms of anticoagulation, such as low-molecular-weight heparin (LMWH), should be considered in some cases in the HIV-infected population receiving antiretroviral therapy, given the absence of compliance in some HIV-affected subjects.

LMWH should be a safer choice in those patients, always keeping in mind that HIV infection may be an independent risk factor for the development of heparin-induced thrombocytopenia (HIT) [44,86]. Lastly the timing of administration of warfarin and certain antiretroviral agents should be staggered.

ERYTHEMA ELEVATUM DIUTINUM

Erythema elevatum diutinum (EED) is emerging as a specific HIV-associated dermatosis. EED is a rare chronic form of localized cutaneous vasculitis that initially presents as leukocytoclastic vasculitis of the skin and later resolves with fibrosis. It is characterized by relapse with or without persistent red, brown-purple, and yellow papules, plaques, and nodules. EED has a predilection for a symmetric distribution over elbows, buttocks, knees, shins, ankles, and interphalangeal joints. Small ulcerations, vesicles, bullae, and lesions resembling xanthomas have less frequently been described.

Epidemiology

Incidence in HIV not known. Occurs usually between fourth to sixth decades.

Pathomechanisms

The pathogenic mechanisms of EED are unknown, but have been described in association with a number of systemic diseases, including infections, autoimmune diseases, and both benign and malignant hematologic disorders. The most commonly associated infections are those due to β-hemolytic streptococci, HBV and HIV [87]. IgA hypergammopathy is also a common finding in HIV infection [88]. One may speculate that the hemorrhagic macules were initially caused by an IgA-associated vasculitis. Because of the induced leakage of the vessel walls, lipid droplets (which were markedly elevated in the serum after ritonavir intake) poured into the perivascular tissue and became phagocytosed by histiocytes. The ongoing inflammation finally induced fibrotic tissue remodeling [89].

Clinical Features

The typical cutaneous lesions of erythema elevatum diutinum are violaceous, red–brown or yellowish papules, plaques or nodules that are in a symmetric distribution and favor the extensor surfaces of the hands and knees. Additional sites of involvement include the buttocks, forearms, head and chest. Initially, the lesions are edematous, and with time they become firm due to fibrosis. In general, the lesions are asymptomatic, but they can be painful or pruritic. (bolognia) Haemorrhage and ulceration are extremely uncommon. Retroauricular and palmoplantar areas are the atypical sites of involvement. On exposure to cold, lesions may be exacerbated and become more erythematous, firm and raised in the evening. Some patients have arthralgia; peripheral ulcerative keratitis has been reported. With time, the lesions may become firmer and develop a yellowish-brown coloration, resembling xanthomata. This eventually heal with dyspigmentation [90]. Juxta articular nodules have been observed in HIV patients.

Pathology

Histopathology reveals a diffuse dermal infiltration of neutrophils and eosinophils. The dermal blood vessels show leukocytoclastic vasculitis features(endothelial swelling, nuclear dust, fibrin deposits). Older lesions may become more granulomatous or even fibrotic. Necrobiosis is not seen. A histologic variant is extracellular cholesterolosis in which there are cholesterol clefts and granulomatous response.

Treatment

Treatment options for EED are limited and disappointing. Dapsone might be beneficial in preventing new lesions [88,91,92] whereas late-stage fibrotic nodules do not respond to this treatment [93,94]. Colchicine has been tried. For large lesions excision can be done. Decreasing hypertriglyceridemia may be important for the general health of the patient, but it has no impact on the lesions [88].

BACILLARY ANGIOMATOSIS

Synonyms: Epithelioid angiomatosis; Disseminated cat scratch disease.

Introduction

Bacillary angiomatosis(BA) is a bacterial infection that may involve any body site, but it usually affects the skin and subcutaneous tissue. Lesions of variable size and shape may be seen, including red to purple 'vascular-appearing' papules or nodules and ulcers. The number of lesions ranges from one to more than hundreds. It has been postulated that a vasoproliferative factor may lead to their formation [95]. The spectrum of Bartonella infections has expanded rapidly since the first HIV-infected patient with bacillary angiomatosis (BA) was described in 1983 by Stoler. In 1989, leBoit and colleagues coined the name "bacillary angiomatosis".

Etiology

BA is an uncommon disease found in AIDS patients with CD4 count less than 50cells/µl. Of the 19 species of Bartonella described until now, only 10 were acknowledged as human pathogens [96]; *B. bacilliformis*, *B. quintana*, and *B. henselae* are the most frequently described [97,98,99]. The associated vascular proliferation may be due to an angiogenic factor produced by B.henselae and B.quintana. It is generally accepted that human infection occurs directly or by an arthropod vector (*Ctenocephallides felis* for *B. henselae*, and still unknown for *B. quintana*) [96]. About 20% give history of cat scratch or bite.

Clinical Features

BA has an incubation period of about 60 days (range, 10-210 days) [100]. BA can present as; 1) dermal lesions 2) subcutaneous nodules (Figure 8.4) and 3) hyperpigmented indurated plaques. Dermal form presents as multiple rapidly growing edematous pyogenic granulomas like papules and nodules that often ulcerate. Size can range from 1mm to many centimeters and are dusky red

with a collarette of scale and peripheral satellite lesions [101]. Sometimes, subcutaneous plaques and nodules develop, but usually the lesions are exudative, eroded and perhaps ulcerated. Hyperpigmented plaques are most commonly seen in African Americans with BA and are oval in shape. Large fungating masses rarely occur [101].

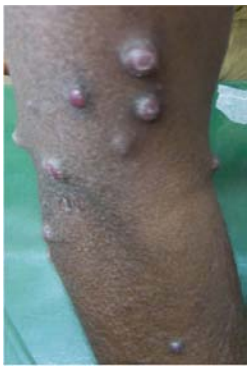

Figure 8.4: Multiple erythematous protuberant papules-to-nodules that tend to bleed very easily.

(Photo courtesy: Dr.Leelavathy B, Department of Dermatology, Bowring and Lady Curzon Hospital)

Associations

Systemic manifestations of BA include lymphadenopathy, constitutional symptoms (fever, night sweats, chills, anorexia, and weight loss), and potentially fatal infections of the heart, bone marrow, gastrointestinal tract, and central nervous system [102-104]. Infection involving the liver and spleen results in a phenomenon known as bacillary peliosis [105]. Ocular lesions can lead to loss of vision.

Laboratory Diagnosis

A ''gold standard'' for diagnosis does not appear to exist, as only small numbers of patients have been reported and multiple methods have been employed. Most of the cases are confirmed by demonstration of the bacilli in histological sections stained with silver dyes (such as the Warthin-Starry method), through serological methods, or through culture propagation. PCR, electron microscopy and culture can also be done [104]. In particular, EM has been useful for confirming the identity of bacilli when staining techniques have been non-diagnostic [102]. The basic histological architecture of BA is a lobular proliferation of endothelium-lined blood vessels within the superficial dermis. Numerous perivascular neutrophilic granulocytes, especially in deeper regions, are also typically present, together with diffuse formation of blood capillaries ("infectious angiogenesis") [104]. Granulomata are rare [104,106]. Histologically Kaposi sarcoma has to be differentiated from BA. The lack of spindle cells, atypically shaped vascular channels and hyaline globules distinguish from Kaposi sarcoma [101].

Differential Diagnosis

- Pyogenic granulomas
- Kaposi's sarcoma
- Cherry angioma
- Angiokeratomas
- Deep fungal infection disseminated to skin

Treatment

Many drugs have been used for the treatment of BA, including doxycycline, trimethoprim-sulphamethoxazole, cephalosporins, aminoglycosides, dapsone, ciprofloxacin, azithromycin or a combination of rifampicin, isoniazid and pyrazinamide [98,104,107,108]. However, the treatment of choice is oral erythromycin [98,109]. Response to this treatment varies from case to case; some cases resolve rapidly, within several days, while others require a prolonged treatment, even for several months, for resolution [104,110].

KAPOSI'S SARCOMA

Kaposi's sarcoma is a spindle cell tumor thought to be derived from endothelilal cell lineage. It is almost a marker for homosexual male HIV/AIDS patients; it is relatively uncommon in all other AIDS risk groups. The single most important factor prior to infection with human herpes virus 8 (discussed in detail in chapter 7).

There are four types of kaposis's sarcoma:

1. Classic type seen in Sub-Saharan Africa
2. Endemic or African kaposi's sarcoma
3. Iatrogenic Kaposi's sarcoma
4. HIV associated kaposi's sarcoma.

AIDS-related KS usually presents with cutaneous and mucus membrane lesions, or lymph node involvement. The tumors most often appear as bluish-red or purple macules, papules, nodules or plaques on the skin. Visceral involvement occurs in 50% of the patients, especially of lungs and gastrointestinal tract [111]. Lung involvement occurs in 20% of the patients and is the most life-threatening form of the disease [112].

The HIV-associated KS usually gets disseminated to the skin, lymph nodes and visceral organs. Common causes of death in AIDS-associated KS are intercurrent illness and systemic involvement especially of the pulmonary system [111]. Histopathology shows numerous slit-like spaces formed by vascular channels dissecting into the collagen of upper and mid-dermis. Extravasation of RBCs

with a moderate superficial and deep perivascular lymphocytic infiltrate along with promontory sign (a small vessel protruding into an abnormal vascular space) are noted [111].

In treatment of HIV-associated KS, HAART forms the mainstay of treatment [111]. Along with HAART, liposomal anthracyclines like doxorubicin are considered as first line systemic therapy for KS because of their good clinical response and relatively few side effects. Paclitaxel is an alternative agent that can induce remission in persons who relapse after anthracycline therapy [111,113]. In countries unable to afford cost of HAART, treatment of KS is likely to be palliative at best [111,114]. In absence of HAART, etoposide was found to be more effective than supportive care or radiotherapy [115].

Treatment and remission of kaposi's sarcoma does not improve survival in AIDS patients. Kaposi's sarcoma indicates poor prognosis.

TELANGIECTASIAS IN HIV

Diffuse Upper Body Telangiectasias Over Chest

Telangiectases have been noted as a cutaneous manifestation of the acquired immunodeficiency syndrome and are characteristically distributed across the upper chest in a crescentic pattern between the clavicles [116]. Facial telangiectasia are also noted. Histopathologic examination shows dermal telangiectasia with perivascular plasma cells.

Periungal Telangiectasia

Periungal telangiectasias is frequently associated with HIV. Although the pathogenesis of periungual telangiectases is not known, Pechère et al. [117], speculated that vascular reactions resulting in periungual erythema might be due to:

a) The association of HIV infection with liver disease induced by hepatitis viruses with immunologic disturbances such as cryoglobulinemia.

b) The angiogenic factors produced by HIV, which have been implicated in the pathogenesis of Kaposi's sarcoma and bacillary angiomatosis, may be responsible for the appearance of telangiectases in patients infected by HIV [118]. These factors include the Tat protein [119,120], interleukin-6, and oncostatin M [121]; oncostatin M is a potent inducer of fusiform cellular morphology [122]. Tat protein could also induce the expression and secretion of fibroblast growth factor, which in turn may act as initiator of angiogenesis and function as a potent mitogen for mesoderm-derived cells [119], and fibroblast growth factor may be potentially relevant to the pathophysiologic development of AIDS–Kaposi's sarcoma [119]. In this way, the angioproliferative diseases described in HIV-infected persons, such as periungual telangiectases, telangiectases in the anterior aspect of the chest, or Kaposi's sarcoma, could be related to Tat protein; this hypothesis is based on the finding that Tat protein also promotes AIDS–Kaposi's sarcoma and normal vascular cells to migrate and to degrade the basement membrane. It also stimulates endothelial cell morphogenesis on a matrix substrate [120].

HYPERALGESIC PSEUDOTHROMBOPHLEBITIS

Definition/Overview

The epitome of a bizarre, HIV-related abnormality of the vasculature, hyperalgesic pseudothrombophlebitis (HP) is a poorly understood, exceedingly rare phenomenon, with only six reports in the HIV literature [123-125].

Pathogenesis/Pathophysiology

Some have speculated that this lesion is a deeply seated KS, as four of the five patients in whom the condition was originally described also had KS. Otherwise, the mechanism of pathology is unknown.

Clinical Features

Patients with this condition typically present with generalized swelling and tenderness of an extremity. No chords are palpable and venous ultrasonography demonstrates patent vessels.

Diagnosis

Doppler ultrasonography and/or venography can be performed to rule out true thrombophlebitis. No laboratory abnormalities are associated with HP.

Management

The condition appears to be self-limiting, according to the cases in the literature. Treatment is supportive with analgesics, warm compresses, bed rest, and extremity elevation [126].

References

1. Bayley AC. Surgical pathology of HIV infection: lessons from Africa. Br J Surg. 1990; 77: 863-868.
2. Joshi VV, Pawel B, Connor E, Sharer L, Oleske JM. Arteriopathy in children with acquired immune deficiency syndrome. Pediatr Pathol. 1987; 7: 261-275.
3. Mulaudzi TV, Robbs JV, Pillay W, Pillay B, Moodley J. Thrombectomy in HIV related peripheral arterial thrombosis: a preliminary report. Eur J Vasc Endovasc Surg. 2005; 30: 102-106.
4. Nair R, Abdool-Carrim A, Chetty R, Robbs J. Arterial aneurysms in patients infected with human immunodeficiency virus: a distinct clinicopathology entity? J Vasc Surg. 1999; 29: 600-607.
5. Nair R, Chetty R, Woolgar J, Naidoo NG, Robbs JV. Spontaneous arteriovenous fistula resulting from HIV arteritis. J Vasc Surg. 2001; 33: 186-187.
6. Nair R, Robbs JV, Chetty R, Naidoo NG, Woolgar J. Occlusive arterial disease in HIV-infected patients: a preliminary report. Eur J Vasc Endovasc Surg. 2000; 20: 353-357.
7. Kaye BR. Rheumatologic manifestations of HIV infections. Clin Rev Allergy Immunol. 1996; 14: 385-416.
8. Calabrese LH. Vasculitis and infection with the human immunodeficiency virus. Rheum Dis Clin North Am. 1991; 17: 131-147.
9. Chetty R. Vasculitides associated with HIV infection. J Clin Pathol. 2001; 54: 275-278.
10. Lie JT. Vasculitis associated with infectious agents. Curr Opin Rheumatol. 1996; 8: 26-29.
11. Munirathnam D, Raj R. Unusual Presentation of HIV Vasculopathy in a Child. Indian J Hematol Blood Transfus. 2011; 27: 169-171.
12. Gisselbrecht M, Cohen P, Lortholary O, Jarrousse B, Gayraud M. HIV-related vasculitis: clinical presentation and therapeutic approach on six patients. AIDS. 1997; 11: 121-123.

13. Kakrani AL, Basavraj A, Madraki R. Vasculitis with digital gangrene in a patient with HIV infection. J Assoc Physicians India. 2003; 51: 299-301.

14. Libman BS, Quismorio FP Jr, Stimmler MM. Polyarteritis nodosa-like vasculitis in human immunodeficiency virus infection. J Rheumatol. 1995; 22: 351-355.

15. Grace M, Job S. Gangrene of the extremities: A rare manifestation of human immunodeficiency virus infection. J HIV Hum Reprod. 2013; 1:41-43.

16. Gherardi R, Belec L, Mhiri C, Gray F, Lescs MC. The spectrum of vasculitis in human immunodeficiency virus-infected patients. A clinicopathologic evaluation. Arthritis Rheum. 1993; 36: 1164-1174.

17. Gocke DJ, Hsu K, Morgan C, Bombardieri S, Lockshin M. Association between polyarteritis and Australia antigen. Lancet. 1970; 2: 1149-1153.

18. Trepo C, Thivolet J. Hepatitis associated antigen and periarteritis nodosa (PAN). Vox Sang. 1970; 19: 410-411.

19. Potashner W, Buskila D, Patterson B, Karasik A, Keystone EC. Leukocytoclastic vasculitis with HIV infection. J Rheumatol. 1990; 17: 1104-1107.

20. Qureshi AI, Janssen RS, Karon JM, Weissman JP, Akbar MS. Human immunodeficiency virus infection and stroke in young patients. Arch Neurol. 1997; 54: 1150-1153.

21. Hoffmann M, Berger JR, Nath A, Rayens M. Cerebrovascular disease in young, HIV-infected, black Africans in the KwaZulu Natal province of South Africa. J Neurovirol. 2000; 6: 229-236.

22. Wu DT, Woodman SE, Weiss JM, McManus CM, D'Aversa TG. Mechanisms of leukocyte trafficking into the CNS. J Neurovirol. 2000; 6 Suppl 1: S82-85.

23. Mandell BF, Calabrese LH. Infections and systemic vasculitis. Curr Opin Rheumatol. 1998; 10: 51-57.

24. Cid MC. New developments in the pathogenesis of systemic vasculitis. Curr Opin Rheumatol. 1996; 8: 1-11.

25. Nair R, Abdool-Carrim A, Chetty R, Robbs J. Arterial aneurysms in patients infected with human immunodeficiency virus: a distinct clinicopathology entity? J Vasc Surg. 1999; 29: 600-607.

26. Botes K, Van Marle J. Surgical intervention for HIV related vascular disease. Eur J Vasc Endovasc Surg. 2007; 34: 390-396.

27. Chetty R, Batitang S, Nair R. Large artery vasculopathy in HIV-positive patients: another vasculitic enigma. Hum Pathol. 2000; 31: 374-379.

28. Mulaudzi T. HIV asscoaited vasculopathy: Vasculopathy is a major feature of HIV disease. CME. 2009; 27: 320-322.

29. Paruk N, Robbs JV, Mulaudzi TV, Pillay B. HIV Vasculopathy. Presentation at VASSA October 2008, Champain Spot Drakensberg Mountains.

30. Nair R, Robbs JV, Naidoo NG, Woolgar J. Clinical profile of HIV-related aneurysms. Eur J Vasc Endovasc Surg. 2000; 20: 235-240.

31. Jenkins RE, Peters BS, Pinching AJ. Thromboembolic disease in AIDS is associated with cytomegalovirus disease. AIDS. 1991; 5: 1540-1542.

32. Laing RB, Brettle RP, Leen CL. Venous thrombosis in HIV infection. Int J STD AIDS. 1996; 7: 82-85.

33. Howling SJ, Shaw PJ, Miller RF. Acute pulmonary embolism in patients with HIV disease. Sex Transm Infect. 1999; 75: 25-29.

34. George SL, Swindells S, Knudson R, Stapleton JT. Unexplained Thrombosis in HIV-infected Patients Receiving Protease Inhibitors: Report of Seven Cases. Am J Med. 1999; 107: 624–626.

35. Sullivan PS, Dworkin MS, Jones JL, Hooper WC. Epidemiology of thrombosis in HIV-infected individuals. The Adult/Adolescent Spectrum of HIV Disease Project. AIDS. 2000; 14: 321-324.

36. Saber AA, Aboolian A, LaRaja RD, Baron H, Hanna K. HIV/AIDS and the risk of deep vein thrombosis: a study of 45 patients with lower extremity involvement. Am Surg. 2001; 67: 645-647.

37. Saif MW, Bona R, Greenberg B. AIDS and thrombosis: retrospective study of 131 HIV-infected patients. AIDS Patient Care STDS. 2001; 15: 311-320.

38. Fultz SL, McGinnis KA, Skanderson M, Ragni MV, Justice AC. Association of venous thromboembolism with human immunodeficiency virus and mortality in veterans. Am J Med. 2004; 116: 420-423.

39. Copur AS, Smith PR, Gomez V, Bergman M, Homel P. HIV infection is a risk factor for venous thromboembolism. AIDS Patient Care STDS. 2002; 16: 205-209.

40. Ahonkhai AA, Gebo KA, Streiff MB, Moore RD, Segal JB. Venous thromboembolism in patients with HIV/AIDS: a case-control study. J Acquir Immune Defic Syndr. 2008; 48: 310-314.

41. Malek J, Rogers R, Kufera J, Hirshon JM. Venous thromboembolic disease in the HIV-infected patient. Am J Emerg Med. 2011; 29: 278-282.

42. Crum-Cianflone NF, Weekes J, Bavaro M. Review: thromboses among HIV-infected patients during the highly active antiretroviral therapy era. AIDS Patient Care STDS. 2008; 22: 771-778.

43. Rasmussen LD, Dybdal M, Gerstoft J, Kronborg G, Larsen CS. HIV and risk of venous thromboembolism: a Danish nationwide population-based cohort study. HIV Med. 2011; 12: 202-210.

44. Bibas M, Biava G, Antinori A. HIV-Associated Venous Thromboembolism. Mediterr J Hematol Infect Dis. 2011; 3: e2011030.

45. Goldhaber SZ1. Risk factors for venous thromboembolism. J Am Coll Cardiol. 2010; 56: 1-7.

46. Wilkerson WR, Sane DC. Aging and thrombosis. Semin Thromb Hemost. 2002; 28: 555-568.

47. Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med. 2008; 5: e203.

48. Anderson JA, Weitz JI. Hypercoagulable states. Clin Chest Med. 2010; 31: 659-673.

49. Lafeuillade A, Alessi MC, Poizot-Martin I, Boyer-Neumann C, Zandotti C. Endothelial cell dysfunction in HIV infection. J Acquir Immune Defic Syndr. 1992; 5: 127-131.

50. Sorice M, Griggi T, Arcieri P, Circella A, d'Agostino F. Protein S and HIV infection. The role of anticardiolipin and anti-protein S antibodies. Thromb Res. 1994; 73: 165-175.

51. de Larrañaga GF, Forastiero RR, Carreras LO, Alonso BS. Different types of antiphospholipid antibodies in AIDS: a comparison with syphilis and the antiphospholipid syndrome. Thromb Res. 1999; 96: 19-25.

52. Feffer SE, Fox RL, Orsen MM, Harjai KJ, Glatt AE. Thrombotic tendencies and correlation with clinical status in patients infected with HIV. South Med J. 1995; 88: 1126-1130.

53. Espinosa G, Cervera R. Antiphospholipid syndrome: frequency, main causes and risk factors of mortality. Nat Rev Rheumatol. 2010; 6: 296-300.

54. Sène D, Piette JC, Cacoub P. Antiphospholipid antibodies, antiphospholipid syndrome and infections. Autoimmun Rev. 2008; 7: 272-277.

55. Funderburg NT, Mayne E, Sieg SF, Asaad R, Jiang W. Increased tissue factor expression on circulating monocytes in chronic HIV infection: relationship to in vivo coagulation and immune activation. Blood. 2010; 115: 161-167.

56. García F, Fumero E, Gatell JM. Immune modulators and treatment interruption. Curr Opin HIV AIDS. 2008; 3: 124-130.

57. Funderburg NT, Mayne E, Sieg SF, Asaad R, Jiang W. Increased tissue factor expression on circulating monocytes in chronic HIV infection: relationship to in vivo coagulation and immune activation. Blood. 2010; 115: 161-167.

58. Morel O, Toti F, Hugel B, Bakouboula B, Camoin-Jau L. Procoagulant microparticles: disrupting the vascular homeostasis equation? Arterioscler Thromb Vasc Biol. 2006; 26: 2594-2604.

59. Mackman N, Tilley RE, Key NS. Role of the extrinsic pathway of blood coagulation in hemostasis and thrombosis. Arterioscler Thromb Vasc Biol. 2007; 27: 1687-1693.

60. Bernasconi E, Uhr M, Magenta L, Ranno A, Telenti A; Swiss HIV Cohort Study. Homocysteinaemia in HIV-infected patients treated with highly active antiretroviral therapy. AIDS. 2001; 15: 1081-1082.

61. Guaraldi G, Ventura P, Garlassi E, Orlando G, Squillace N. Hyperhomocysteinaemia in HIV-infected patients: determinants of variability and correlations with predictors of cardiovascular disease. HIV Med. 2009; 10: 28-34.

62. Gresele P, Momi S, Migliacci R. Endothelium, venous thromboembolism and ischaemic cardiovascular events. Thromb Haemost. 2010; 103: 56-61.

63. Migliacci R, Becattini C, Pesavento R, Davi G, Vedovati MC. Endothelial dysfunction in patients with spontaneous venous thromboembolism. Haematologica. 2007; 92: 812-818.

64. Gresele P, Migliacci R, Vedovati MC, Ruffatti A, Becattini C, et al. Patients with primary antiphospholipid antibody syndrome and without associated vascular risk factors present a normal endothelial function. Thromb Res. 2009; 123: 444–451.

65. Pomerantz RJ, Kuritzkes DR, de la Monte SM, Rota TR, Baker AS. Infection of the retina by human immunodeficiency virus type I. N Engl J Med. 1987; 317: 1643-1647.

66. Solages A, Vita JA, Thornton DJ, Murray J, Heeren T. Endothelial function in HIV-infected persons. Clin Infect Dis. 2006; 42: 1325-1332.

67. Chi D, Henry J, Kelley J, Thorpe R, Smith JK. The effects of HIV infection on endothelial function. Endothelium. 2000; 7: 223-242.

68. Sullivan PS, Dworkin MS, Jones JL, Hooper WC. Epidemiology of thrombosis in HIV-infected individuals. The Adult/Adolescent Spectrum of HIV Disease Project. AIDS. 2000; 14: 321-324.

69. Klein SK, Slim EJ, de Kruif MD, Keller TT, ten Cate H. Is chronic HIV infection associated with venous thrombotic disease? A systematic review. Neth J Med. 2005; 63: 129-136.

70. Karpatkin S, Nardi M, Green D. Platelet and coagulation defects associated with HIV-1-infection. Thromb Haemost. 2002; 88: 389-401.

71. Baker JV, Neuhaus J, Duprez D, Kuller LH, Tracy R, et al. Changes in Inflammatory and Coagulation Biomarkers: A Randomized Comparison of Immediate versus Deferred Antiretroviral Therapy in Patients With HIV Infection. J Acquir Immune Defic Syndr. 2011; 56: 36-43.

72. Abgueguen P, Delbos V, Chennebault JM, Payan C, Pichard E. Vascular thrombosis and acute cytomegalovirus infection in immunocompetent patients: report of 2 cases and literature review. Clin Infect Dis. 2003; 36: E134-139.

73. White NW. Venous thrombosis and rifampicin. Lancet. 1989; 2: 434–435.

74. Ambrosetti M, Ferrarese M, Codecasa LR, Besozzi G, Sarassi A. Incidence of venous thromboembolism in tuberculosis patients. Respiration. 2006; 73: 396.

75. Khorana AA, Connolly GC. Assessing risk of venous thromboembolism in the patient with cancer. J Clin Oncol. 2009; 27: 4839-4847.

76. Scates SM. Diagnosis and treatment of cancer-related thrombosis. Hematol Oncol Clin North Am. 1992; 6: 1329-1339.

77. Engels EA, Pfeiffer RM, Goedert JJ, Virgo P, McNeel TS. Trends in cancer risk among people with AIDS in the United States 1980-2002. AIDS. 2006; 20: 1645-1654.

78. Engels EA, Biggar RJ, Hall HI, Cross H, Crutchfield A. Cancer risk in people infected with human immunodeficiency virus in the United States. Int J Cancer. 2008; 123: 187-194.

79. Schneider E, Whitmore S, Glynn KM, Dominguez K, Mitsch A. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years--United States, 2008. MMWR Recomm Rep. 2008; 57: 1-12.

80. Kaufmann T, Nisce LZ, Metroka C. Thromboembolism in AIDS-related Kaposi's sarcoma. JAMA. 1991; 266: 2834.

81. Shiels MS, Pfeiffer RM, Gail MH, Hall HI, Li J. Cancer burden in the HIV-infected population in the United States. J Natl Cancer Inst. 2011; 103: 753-762.

82. Barbaro G. Cardiovascular manifestations of HIV infection. Circulation. 2002; 106: 1420-1425.

83. Force L, Barrufet P, Herreras Z, Bolibar I. Deep venous thrombosis and megestrol in patients with HIV infection. AIDS. 1999; 13: 1425-1426.

84. Nagaraja V, Terriquez JA, Gavini H, Jha L, Klotz SA. Pulmonary Embolism Mimicking Pneumonia in a HIV Patient. Case Rep Med. 2010; 2010: 394546.

85. Fulco PP, Zingone MM, Higginson RT. Possible antiretroviral therapy-warfarin drug interaction. Pharmacotherapy. 2008; 28: 945-949.

86. Thompson GR 3rd, Lawrence VA, Crawford GE. HIV infection increases the risk of heparin-induced thrombocytopenia. Clin Infect Dis. 2007; 45: 1393-1396.

87. Chung L, Kea B, Fiorentino DF. Cutaneous Vasculitis. In: Bolognia JL, Jorizzo JL, Rapini RP, editors. Dermatology. Spain: Elsevier publication;2008. 356.

88. Chowdhury MM, Inaloz HS, Motley RJ, Knight AG. Erythema elevatum diutinum and IgA paraproteinaemia: 'a preclinical iceberg'. Int J Dermatol. 2002; 41: 368-370.

89. Braun-Falco M, Hofmann H. An HIV-positive man with slowly enlarging nodules on the extremities. Clin Infect Dis. 2007; 44: 976, 1009-1010.

90. Comfere NI, Gibson LE. Erythema elevatum diutinum. In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, et al, editors. Fitzpatrik's dermatology in general medicine. New York: McGraw-Hill. 2012.

91. Martín JI, Dronda F, Chaves F. Erythema elevatum diutinum, a clinical entity to be considered in patients infected with HIV-1. Clin Exp Dermatol. 2001; 26: 725-726.

92. Suárez J, Miguélez M, Villalba R. Nodular erythema elevatum diutinum in an HIV-1 infected woman: response to dapsone and antiretroviral therapy. Br J Dermatol. 1998; 138: 717-718.

93. LeBoit PE, Cockerell CJ. Nodular lesions of erythema elevatum diutinum in patients infected with the human immunodeficiency virus. J Am Acad Dermatol. 1993; 28: 919-922.

94. Muratori S, Carrera C, Gorani A, Alessi E. Erythema elevatum diutinum and HIV infection: a report of five cases. Br J Dermatol. 1999; 141: 335-338.

95. Halpern AV, Heymann WR. Bacterial diseases. In: Bolognia JL, Jorizzo JL, Rapini RP, editors. Dermatology. Spain: Elsevier. 2008; 1096.

96. Bernabeu-Wittel J, Luque R, Corbi R, Mantrana-Bermejo M, Navarrete M. Bacillary angiomatosis with atypical clinical presentation in an immunocompetent patient. Indian J Dermatol Venereol Leprol. 2010; 76: 682-685.

97. Spach DH, Koehler JE. Bartonella-associated infections. Infect Dis Clin North Am. 1998; 12: 137-155.

98. Maguiña C, Gotuzzo E. Bartonellosis. New and old. Infect Dis Clin North Am. 2000; 14: 1-22, vii.

99. Pons I, Sanfeliu I, Quesada M, Anton E, Sampere M. Prevalence of Bartonella henselae in cats in Catalonia, Spain. Am J Trop Med Hyg. 2005; 72: 453-457.

100. Pons I, Sanfeliu I, Quesada M, Anton E, Sampere M. Prevalence of Bartonella henselae in cats in Catalonia, Spain. Am J Trop Med Hyg. 2005; 72: 453-457.

101. Maguiña C, Guerra H, Ventosilla P. Bartonellosis. Clin Dermatol. 2009; 27: 271-280.

102. Berger TG, Bravo FG. Bartonellosis. In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller As, et al., editors. Fitzpatrick's Dermatology in general medicine. New York: McGraw-Hill. 2012.

103. Amsbaugh S, Huiras E, Wang NS, Wever A, Warren S. Bacillary angiomatosis associated with pseudoepitheliomatous hyperplasia. Am J Dermatopathol. 2006; 28: 32-35.

104. Webster GF, Cockerell CJ, Friedman-Kien AE. The clinical spectrum of bacillary angiomatosis. Br J Dermatol. 1992; 126: 535-541.

105. Albayrak A, Albayrak Y, Unal D, Atasoy M, Uyanik MH. A case of bacillary angiomatosis developed at a burn site. Indian J Dermatol Venereol Leprol. 2012; 78: 121.

106. Mohle-Boetani JC, Koehler JE, Berger TG, LeBoit PE, Kemper CA, et al. Bacillary angiomatosis and bacillary peliosis in patients infected with human immunodeficiency virus: Clinical characteristics in a case-control study. Clin Infect Dis. 1996; 22: 794-800.

107. Maguiña C, Guerra H, Ventosilla P. Bartonellosis. Clin Dermatol. 2009; 27: 271-280.

108. Schwartz RA, Nychay SG, Janniger CK, Lambert WC. Bacillary angiomatosis: presentation of six patients, some with unusual features. Br J Dermatol. 1997; 136: 60-65.

109. Smith DL. Cat-scratch disease and related clinical syndromes. Am Fam Physician. 1997; 55: 1783-1789, 1793-4.

110. Webster GF, Cockerell CJ, Friedman-Kien AE. The clinical spectrum of bacillary angiomatosis. Br J Dermatol. 1992; 126: 535-541.

111. Rudikoff D, Phelps RG, Gordon RE, Bottone EJ. Acquired immunodeficiency syndrome-related bacillary vascular proliferation (epithelioid angiomatosis): Rapid response to erythromycin therapy. Arch Dermatol. 1989; 125:706-707.

112. Kharkar V, Gutte RM, Khopkar U, Mahajan S, Chikhalkar S. Kaposi's sarcoma: a presenting manifestation of HIV infection in an Indian. Indian J Dermatol Venereol Leprol. 2009; 75: 391-393.

113. Krown SE. Acquired immunodeficiency syndrome-associated Kaposi's sarcoma. Biology and management. Med Clin North Am. 1997; 81: 471-494.

114. Ziegler JL, Newton R, Katongole-Mbidde E, Mbulataiye S, De Cock K. Risk factors for Kaposi's sarcoma in HIV-positive subjects in Uganda. AIDS. 1997; 11: 1619-1626.

115. Lynen L, Zolfo M, Huyst V, Louis F, Barnardt P. Management of Kaposi's sarcoma in resource-limited settings in the era of HAART. AIDS Rev. 2005; 7: 13-21.

116. Olweny CL, Borok M, Gudza I, Clinch J, Cheang M. Treatment of AIDS-associated Kaposi's sarcoma in Zimbabwe: results of a randomized quality of life focused clinical trial. Int J Cancer. 2005; 113: 632-639.

117. MacFarlane DF, Gregory N. Telangiectases in human immunodeficiency virus-positive patients. Cutis. 1994; 53: 79-80.

118. Pechère M, Krischer J, Rosay A, Hirschel B, Saurat JH. Red fingers syndrome in patients with HIV and hepatitis C infection. Lancet. 1996; 348: 196-197.

119. Ruiz-Avila P, Tercedor J, Fuentes E, Villar A, Ródenas JM. Painful periungual telangiectasias in a patient with acquired immunodeficiency syndrome. Int J Dermatol. 1995; 34: 199-200.

120. Opalenik SR, Shin JT, Wehby JN, Mahesh VK, Thompson JA. The HIV-1 TAT protein induces the expression and extracellular appearance of acidic fibroblast growth factor. J Biol Chem. 1995; 270: 17457-17467.

121. Albini A, Barillari G, Benelli R, Gallo RC, Ensoli B. Angiogenic properties of human immunodeficiency virus type 1 Tat protein. Proc Natl Acad Sci U S A. 1995; 92: 4838-4842.

122. Nair BC, DeVico AL, Nakamura S, Copeland TD, Chen Y. Identification of a major growth factor for AIDS-Kaposi's sarcoma cells as oncostatin M. Science. 1992; 255: 1430-1432.

123. Miles SA, Martínez-Maza O, Rezai A, Magpantay L, Kishimoto T. Oncostatin M as a potent mitogen for AIDS-Kaposi's sarcoma-derived cells. Science. 1992; 255: 1432-1434.

124. Stoff BK, Calame A, Cockerall CJ. Non-neoplastic disorders of vasculature in HIV infection. In: Cockerall CJ, Calame A, editors. Cutaneous manifestations of HIV Disease. London: Manson Publishing. 2012.

125. Abramson SB, Odajnyk CM, Grieco AJ, Weissmann G, Rosenstein E. Hyperalgesic pseudothrombophlebitis. New syndrome in male homosexuals. Am J Med. 1985; 78: 317-320.

126. Monfort-Gouraud M, Duyckaerts V, Boccara F, de Boissieu D, Guillou MA. [Superficial pseudophlebitis in a HIV seropositive child]. Arch Fr Pediatr. 1991; 48: 205-206.

127. Monfort-Gouraud M, Duyckaerts V, Boccara F, de Boissieu D, Guillou MA. [Superficial pseudophlebitis in a HIV seropositive child]. Arch Fr Pediatr. 1991; 48: 205-206.

128. Friedman-Kien AE, Cockerell CJ. Cutaneous manifestation of HIV infection: vasculitis and other vascular-related abnormalities. In: Alvin E Friedman-Kien, Clay J Cockerell, editors. Color Atlas of AIDS, 2nd edn. Philadelphia: WB Saunders. 1996; 134–135..