

Challenges of extensive AIDS-related dry gangrene during COVID-19 pandemic: a case report and mini review

Manuela Arbune^{1,2,#}, Diana Sabina Radaschin^{1,3,#}, Sabina Ganea², Caterina Nela Dumitru^{1,4}

¹Faculty of Medicine and Pharmacy, Research Centre in the Field of Medical and Pharmaceutical Sciences (ReForm-UDJ), "Dunărea de Jos" University of Galați, Romania

²Department of Infectious Diseases, Infectious Diseases Clinical Hospital, Galati, Romania

³Multidisciplinary Integrated Centre of Dermatological Interface Research Centre (MICDIR), "Dunarea de Jos" University of Galati, Romania

⁴Laboratory Department, Infectious Diseases Clinical Hospital, Galati, Romania

[#]These authors contributed equally to this work.

Abstract

Introduction: The common aetiologies of gangrene are atherosclerosis and diabetes mellitus, while human immunodeficiency virus (HIV) can be one of additional various pathologic conditions. The risk of peripheral arterial disease is higher in HIV-infected population. Almost every pattern and type of vasculitis were described in HIV people, but widespread digital ischemic changes and gangrene of the hands and feet are uncommon presentations.

Case presentation: We presented a case of a 33-year-old patient from HIV pediatric Romanian cohort, homeless, previous smoker, and drug user. He was diagnosed HIV-positive 28 years ago, and experienced severe opportunistic diseases and multiple failures of antiretroviral treatments. Clinical examination revealed blackish discoloration in both legs and feet, and severe immunosuppression. Debridement, necrotomy, and lavage of the legs were done, and he received directly observed antiretrovirals. The patient was infected with COVID-19. After 24 weeks, the viral load was undetectable, CD4 count increased, and no necrosis observed, but he is totally care-dependent.

Conclusions: HIV people are vulnerable during COVID-19 pandemic due to the limited access to health-care and high-risk of COVID-19-associated infections. Gangrene is a rare condition associated with HIV demonstrating poor functional prognosis, even with viral suppression achieved after antiretroviral treatment.

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Key words: vasculitis, HIV/AIDS, gangrene, antiretroviral therapy, COVID-19.

Introduction

Gangrene represents tissue necrosis due to ischemia or infection. Necrosis affects the skin, subcutaneous tissue, fascia, and muscular structures. Clinically, the tissue is character-

ized by discolored or black appearance, and it can be circumferential at the level of fingers or extremities of the limbs.

There are three clinically known forms of gangrene, i.e., dry gangrene, wet gangrene, and gaseous gangrene. The dry type is usually considered a consequence of peripheral arterial

Address for correspondence: Manuela Arbune,
Department of Clinical Medical, "Dunărea de Jos" University
of Galați, Romania, Domneasca, 47, 800008, Galati, Romania,
e-mail: manuela.arbune@ugal.ro

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disease, and is characterized by distal ischemia and dehydration of tissue due to arterial occlusion [1]. Dry gangrene arises because of peripheral arterial occlusion secondary to atherosclerosis, and have the same risk factors as coronary artery disease, including tobacco use, high blood pressure, diabetes, and hyperlipemia. Ischemic events can be intensified by trauma and infections, but most studies suggest that dry gangrene is mostly aseptic. Other causes of ischemia are arterial thrombosis associated with hypercoagulability or predisposing diseases, such as vasculitis [2].

Gangrene of the extremities in people with human immunodeficiency virus (HIV) infection is scarcely documented in medical literature. The pathogenic mechanisms of vascular lesions associated with HIV can be explained by direct microbial invasion of the vascular wall or by immune-mediated lesions [3].



Figure 1. Left foot: Dry gangrene of toes, erosions, and HIV-associated dry ulcerations



Figure 2. Left foot: Dry gangrene of II-V digits, non-healing plantar ulceration, necrosis, and HIV-associated fibrotic deposition

Case presentation

We presented a case of 33-year-old HIV-positive homeless patient, previous smoker, and occasional drug user. The patient was brought by police into the emergency service due to epileptic seizure. He was admitted to the nephrology department to compensate for an acute renal failure syndrome (GFR: 15.7 ml/min). After 3 weeks, the patient was transferred to the infectious diseases department for HIV evaluation and treatment. Clinical examination revealed BP of 120/80 mmHg, RR of 20/min, HR of 80/min, SO_2 of 96%; he was afebrile, disoriented, immobilized with left hemiparesis, bilateral exophthalmia with right eye cataract, conjunctival hyperemia, and decreased visual acuity in the left eye. Dry skin, muco-cutaneous lichen planus, and dry gangrene's necrotic lesions of both lower limbs, comprising legs and 1/3 of lower calves, were also observed (Figures 1-3).

It was not possible to obtain gangrene's historical data, but frostbite was excluded due to warm season. The patient was confirmed with HIV/AIDS in another city; he abandoned antiretroviral therapy and was lost to follow-up during the first year of the COVID-19 pandemic.

Investigation of the patient medical history found data confirming the diagnosis of HIV at the age of 5 when he had lymph nodes tuberculosis, as a marker of immunodepression. The patient was part of the HIV pediatric cohort in Romania, characterized by nosocomial infection during 1988-1990, when many infants from seronegative mothers were diagnosed with HIV. After HIV diagnosis, he was abandoned and cared for in a children's institution until the age of majority. The patient had no relatives, and was homeless



Figure 3. Right foot: Atrophic scars, non-healing ulcerations with hematic crusts, auto-amputation of 3 digits, and HIV-associated onychodystrophy

after failure of social interventions and integration into different centers.

Post-HIV diagnosis, he experienced significant events, including viral meningitis, measles, renal lithiasis, severely evolving cerebral toxoplasmosis (with coma), relapse and sequelae (facial nerve paresis, right hemiparesis, epileptic seizures, dysarthria, and right eye exophthalmia), tuberculous pleurisy (abandoned treatment), and bilateral nodular infiltrative secondary tuberculosis (completed treatment). Moreover, apart from diagnoses of HIV encephalopathy and progressive neurocognitive dysfunction with behavioral and relational disorders, he suffered from chronic prurigo, lichen planus, recurrent candidiasis, herpes simplex, and herpes zoster (Figure 4). The patient received several combinations of antiretroviral therapies, which were continually abandoned.

Laboratory evaluation revealed severe immunodepression (CD4: 34/mm³), high viral replication rate of 328,000 c/ml, anemia, hypoalbuminemia, nitrogen retention, inflammatory syndrome, and increased D-dimers. Co-infection markers were negative for syphilis and HCV, but positive for HBV (HBsAg, IgG HBc-Ab-negative, undetectable HBV DNA), and negative for IgG HDV-Ab. Tests evaluating thrombophilia profile were within normal limits, including IgG anticardiolipin antibodies, IgM, anti-beta2 antibodies glycoprotein 1 IgG, IgM, IgA, protein C, activated S protein, antithrombin III, and lupus anticoagulant (Table 1).

Necrotic lesions were treated conservatively by repeated partial necrectomy, lavage, and local dressing. Deep tissue lesions affected osteo-tendinous structures of the foot (Achilles'

tendons, anterior tibiofibular, and superficial plantar fascia), and the left foot had self-amputated 1-5 fingers and 2-3 fingers of the right foot. For HIV infection, he received antiretroviral treatment (ARV) with doravirine + lamivudine + tenofovir, and obtained complete viral suppression after 6 months, subsequently supported by the same therapy. The increase of CD4 lymphocyte count was sub-optimal due to persistent values below 200/mm³ after 12 months. Inflammation and coagulation markers improved, although remained above normal values corresponding to age.

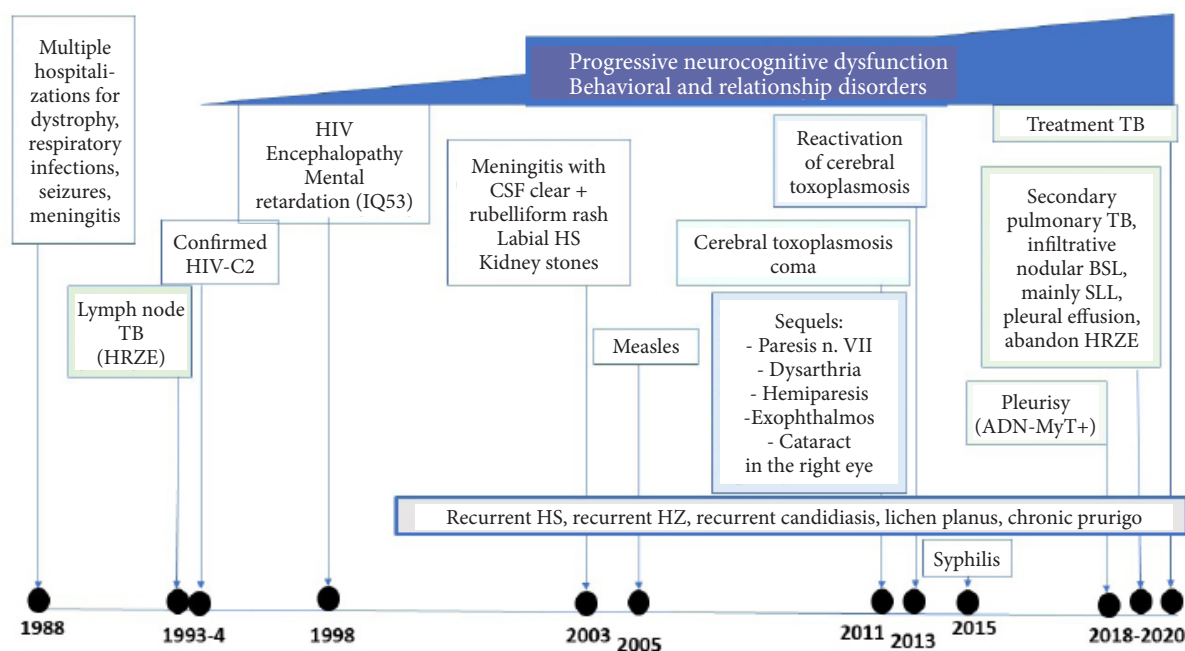
Due to prolonged hospitalization and during the third wave of COVID-19 pandemic, he developed a mild form of COVID-19 but post-infection, he experienced transient ischemic stroke and epileptic crisis.

After one year, clinical and laboratory assessments revealed persistent viral suppression, moderate lymphocytic depletion, removal of skin necrosis and soft parts from the limbs with partial re-epithelization (after topical treatments), and loss of the legs functionality and atrophy of the limbs' muscles. General condition was good, but memory disorders increased, he has no vision (cataract in the left eye and uveitis in the right eye), cannot walk, and is completely care-dependent.

Discussion

As seen in Table 2, peculiar features are identified in HIV-associated gangrene.

Although previous epidemiological data validated that antiretrovirals could increase life expectancy of people living



BSL – bilateral superior lobes, CSF – cerebrospinal fluid, HIV – human immunodeficiency virus, HRZE – izoniazid-rifampin-pyrazinamide-ethambutol, HS – herpes simplex virus, HZ – herpes zoster virus, SLL – superior left lobe, TB – tuberculosis

Figure 4. Medical history of a HIV-positive male patient, nosocomially infected with dry gangrene in early childhood

Table 1. Biological tests' dynamics of HIV-positive male with dry gangrene

	1 wk.	4 wk.	8 wk.	COVID-19			12 wk.	16 wk.	20 wk.	24 wk.
Hemoglobin (13-17 g/dl)	10.0	10.1	10.5	9.7	10.3	9.9	11.7	11.1	11.6	13.6
Thrombocytes (150-450/ μ l)	290	260	212	264	192	322	304	343	223	162
Leucocytes (4-10 \times 10 ³ / μ l)	5.2	5.7	4.7	3.0	3.0	3.3	5.3	5.7	4.1	4.5
Neutrophils (2-7.5/10 ³ / μ l)	4.6	4.1	2.8	1.56	2.07	1.50	3.5	3.6	2.7	2.7
Lymphocytes (1.00-4.00 \times 10 ³ / μ l)	0.4	1.03	1.2	1.07	0.82	1.25	1.1	1.1	0.6	0.88
CD4 (700-1,100 μ l)	34		84				100		78	134
HIV-1 RNA (copies/ml)							201		130	NED
C-reactive protein (CRP) (0-5 mg/l)	46.68	19.12	107.80	64.41	60.27	28.07	31.70	13.36	64.50	19.30
Erythrocytes sedimentation rate (0-15 mm/h)	115	120	120	130			80	84	84	64
Fibrinogen (196-372 mg/dl)	458	380	565	552	496		426	380	478	372
IL-6 (0-17 pg/ml)	30.05					7.71				
Blood glucose (74-106 mg/dl)	137.7	114.5	89.4	87.6	85.8	83.3	89.4	82.4	118.4	95.3
Creatinine (0.8-1.3 mg/dl)	1.26	1.23	1.22	1.33	1.31	1.19	1.50	1.29	1.42	1.30
Urea (19-44 mg/dl)	111.6	47.1	62.2	46.8	52.3	51.0	53.0	51.2	45.9	70.3
ALAT (0-45 U/l)	45.9	102.9	138	64.1	47.1	18.4	16.7	48.8	34.9	23.9
ASAT (0-35 U/l)	78.7	68.3	117.5	53.9	40.5	22.0	24.2	39.0	41.1	24.6
Conjugated bilirubin (0-0.2 mg/dl)	0.24	0.1	0.12	0.09	0.09	0.08	0.09	0.07	0.09	0.11
Alkaline phosphatase (56-119 U/l)	237.3	219.4	243.9	204.4	231.7	179.1		149.2		147.8
Albumin (3.2-5.3 g/dl)	2.98	3.28	3.08						3.35	4.13
Troponin (0-25 ng/l)	4.6			7.4	3.8	< 1.5		< 1.5		
D-dimers (0-500 ng/ml)	1,448	2,565	6,280	5,777	3,766	2,690	1,649	1,113	916	
Ferritin (30-350 ng/ml)	1,084	744	927	817	1,200	619	429	407	340	

Table 2. Peculiarities of gangrene in HIV-infected patient

1.	Gangrene occurred in a patient with pediatric nosocomial HIV infection, which developed for nearly three decades, associated with multiple opportunistic infections and non-AIDS co-morbidities
2.	Prolonged and severe immunosuppression was the consequence of a lack of therapeutic adherence to which neurocognitive disorders, lack of adaptation, and social condition contributed
3.	The appearance of gangrene could be the consequence of peripheral arteriopathy associated with HIV, constituted by atherogenic mechanisms, but also by direct endothelial lesions caused by infectious agents or vessels and skin drug toxicity
4.	The patient with gangrene had a young chronological age, but HIV infection associated early aging, a consequence of inflammation and hypercoagulable status
5.	Functional sequelae after gangrene of the limbs significantly limited quality of life of this HIV-infected patient, which required support through sustained psycho-social interventions, complex functional recovery, cardiovascular monitoring, and HIV management, within a multidisciplinary team

with HIV (PLWH), the patients are more susceptible to developing comorbidities, such as cancer, and liver, renal, bone, and cardiovascular diseases, comparing with HIV-negatives [4].

Inflammation represents the key point of these aging-related comorbidities, attributed to HIV replication, ARV toxicity, loss of regulatory cells, co-infections, such as CMV, and microbial translocation [5]. Inflammation induces the activation of monocytes, T lymphocytes, and has been

observed to increase endothelium adhesion, dyslipidemia, and hypercoagulation. The current antiretroviral therapies impair viral replication, but do not eradicate the virus. Although undetectability is attained, the viral reservoirs are correlated with remaining persistent inflammation. In virologically suppressed patients, immune dysfunction persists, even if there is a normalization of CD4 count. Large cohort studies evidenced elevated biomarkers of immune activa-

tion, such as IL-6, sCD14, and D-dimer, which are associated with mortality [6].

Immune activation markers in PLWH have been linked with accelerate biological aging, atherosclerosis, higher risk of cardiovascular diseases, kidney chronic disease, neuro-cognitive disorders, and other non-AIDS comorbidity risks. This relation was proven in both treatment-naïve and experienced patients, though immune activation in PLWH decreased under antiretroviral therapy regardless of combination [7, 8].

Cardiovascular risk and hypercoagulable state in PLWH are amplified due to inflammation and HIV itself. Although ART improves the coagulation balance, normal level is difficult to obtain [9]. Similarly to the general population, hypertension, lipid disorders, diabetes, and smoking are factors increasing atherosclerosis risk, ischemia, plaque rupture, and consecutive myocardial infarction and stroke, with global amplification of 100% cardiovascular events. Additionally, 19% of peripheral artery diseases, 50% of myocardial infarctions, 17-21% of strokes, 14% of sudden deaths, and 41% of heart failures, are observed in PLWH compared with the general population [10, 11].

The peripheral arterial disease in PLWH has been reported more prevalent, with a six-fold higher risk and an earlier onset than in the general population [12]. In an outpatient rheumatology, extensive retrospective study (1994-2019), 0.9% of HIV-infected patients had some form of vasculitis [13].

A 10-yearlong study conducted in India among 1,311 patients evaluated for HIV infection, reported 2 cases of gangrene in the lower limbs [14]. In severe immunosuppressed HIV patients, endothelial alteration is sporadic, usually implicating opportunistic infections. In addition, there have been reported cases of infectious vasculitis produced by herpes zoster virus, toxoplasmosis, salmonellosis, pneumocystosis, and cytomegalovirus [15, 16].

Conclusions

The limited availability of medical services during the COVID-19 pandemic have influenced therapeutic adherence, and delayed diagnosis and treatment of diverse comorbidities.

Dry gangrene of the limbs is a rare condition in HIV-infected patients, with the following cumulative vascular factors: immunosuppression, chronic endothelial inflammation, drug toxicity, smoking, and non-adherence to antiretroviral treatment. Poor prognosis in functional locomotor and neurological disorders is mostly immunological. Contrary to undetectable HIV viral load and immunological recovery under directly observed antiretroviral therapy, poor prognosis in functional locomotor as well as vascular and neurological disorders are predictable.

Disclosures

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4. Conflicts of interest: None.

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