Urticaria Pigmentosa in a Patient with Acquired Immunodeficiency Syndrome – a case report

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Abstract

The authors present a case of a man with urticaria pigmentosa and acquired immunodeficiency syndrome - AIDS. The patient was diagnosed as HIV (human immunodeficiency virus) - positive in the year 2000, at the Infectious Diseases Clinic, Clinical Center of Vojvodina in Novi Sad. Urticaria pigmentosa was detected (nine years later) during a dermatological examination at the Dermatovenereology Department of the Outpatient Clinic, Clinical Center of Vojvodina. Urticaria pigmentosa is the most common manifestation of cutaneous mastocytosis. The patient was taking long term antiviral therapy for several years. Approximately 2 years after the onset of urticaria pigmentosa, this patient developed septicemia and ascites along with hepatosplenomegaly, liver damage, chronic cholecystitis, leukopenia, thrombocytopenia and relative eosinophilia. The patient had increased total serum IgE levels and tested positive for 5-hydroxyindoleacetic acid in a 24-hour urine test from the very beginning of urticaria pigmentosa and during the course of his illness. Immunohistochemical results of dermal biopsy of the affected area confirmed the diagnosis of urticaria pigmentosa. Histology findings confirmed presence of typical dermal mast cell infiltrates with distinct oval and spindle granules that were CD117+ and CD1a-. Systemic mastocytosis was excluded by liver and bone marrow biopsies. To our knowledge, we present the third case of associated mastocytosis and acquired immunodeficiency syndrome published in world literature so far, in order to indicate the possible interaction between HIV infection and mast cells.

Key words

Urticaria Pigmentosa; HIV; Acquired Immunodeficiency Syndrome; Comorbidity

Urticaria pigmentosa is the most common manifestation of cutaneous mastocytosis in children and adults. In children cutaneous mastocytosis can recur, but may also spontaneously involute (1, 2, 3, 4, 5, 6, 7). The clinical picture differs in childhood and adulthood, both regarding the course and prognosis (1,2). Typical clinical manifestations of urticaria pigmentosa are symmetrically distributed yellowish-brown macules or red papular skin changes. The hairy part of the head, hands, feet and face may be spared. Mucosa is rarely affected. Mild irritation (rubbing or scratching) causes release of inflammatory response mediators (histamine, prostaglandins, leukotrienes, cytokines) causing urtica on the irritated site, which is referred to as the Darier’s sign (1, 2, 5, 6, 7).

As far as we are concerned, this is a rather peculiar case report, since it represents only the third report of associated acquired immunodeficiency syndrome and mastocytosis in the world literature (8,9); furthermore it arises the question whether this association develops due to possible immunogenetic disorders and immunogenetic rearrangements.
Case report

A male patient 36 years of age, an employed worker, single, with HIV confirmed in the year 2000, was initially diagnosed with idiopathic thrombocytopenia. The patient was taking the same highly active antiretroviral therapy (HAART): ddI (didanosine), 3TC (lamivudine), EFV (efavirenz). His CD4 lymphocyte blood count has been stable ever since (with approximately 300 cells/ml), while HIV Ribonucleic acid (RNA) was undetected in his blood via polymerase chain reaction (PCR). The onset of symptoms occurred approximately 2 years before, when yellowish-brown macules and red papular skin changes appeared mostly on his torso and upper extremities, occasionally followed by severe itching and redness when scratched. These symptoms intensified in Fall 2009, when the patient was admitted to the Dermatovenerology Department of the Outpatient Clinic, Clinical Center of Vojvodina. The examination revealed many yellowish-brown maculopapular efl orescences on the torso and upper extremities, associated with severe itching, and a positive Darier’s sign (Figures 1 and 2). A punch biopsy was performed by a dermatologist in order to clarify skin changes. Ten days later, the patient was admitted to the Infectious Diseases Clinic due to high fever (up to 39 degrees celsius) and abdominal pain. *Streptococcus agalactiae* was isolated using hemoculture. Inflammatory parameters were lowered by appropriate antibiotic therapy and the patient felt better. However, there was a sudden development of ascites. Control blood CD4 count was decreased (198/ml), while HIV RNA PCR still showed negative results. Symptomatic therapy lead to disappearance of ascites, but splenomegaly persisted.

During 2009, the patient was hospitalized at the Infectious Diseases Clinic, Clinical Center of Vojvodina in Novi Sad four more times, in 2010 six times, and in 2011 on two occasions, when systemic mastocytosis was excluded. The patient had to receive the same highly active antiretroviral HAART therapy, but desloratadine 5mg/day was added as well.

**Personal history.** Hypersensitivity to various food allergenes. Other problems include irregular bowel movement and diarrhea.

**Family history.** Negative.

**Physical examination.** Upon skin examination, yellowish-brown macules and a large number of reddish papules, up to 5mm in size, with a positive Darier’s sign were found mainly on the abdomen, chest, back, arms and legs (Figures 1 and 2). No changes were found on patient’s mucosa and lips.

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**Figure 1.** Urticaria pigmentosa in an AIDS patient

**Figure 2.** Darier’s sign
Laboratory and other test results

Laboratory test revealed the following abnormal results: Leukopenia (low WBC 2.70 x 10^9/L, normally 4-10x10^9/L), thrombocytopenia (78,1 x 10^9/L, normally 140-400 x 10^9/L), relative eosinophilia [0,316 x 10^9/L (normally > 0.470 x 10^9/L); 11.7% of the total white blood count (normally 0-5%)], slightly elevated transaminase activity (ALT 47 UI/mL, AST 56 UI/mL) along with slightly elevated alkaline phosphatase levels 218 U/I (normally < 198 U/I); increased gamma glutamyl transpeptidase levels (223 IU/mL); hemostatic mechanism within reference values (APTT 0.88; PT 1.91; TT 1,10, D-dimer 110); total serum proteins 76 g/l; serum protein electrophoresis indicated hypergammaglobulinemia of 24.9 g/L (normally 7-16 g/L); other basic laboratory test results were normal.

Positive finding of 5-hydroxyindoleacetic acid - 5-HIAA in the 24-hour urine test: 46.9 µmol/dU (reference range 10,4-31.2 µmol/dU).

Total IgE serum levels: significantly increased 1425 IU/ml (reference value 100 IU/ml).

Histopathological result from September 2009:
A skin fragment was histologically examined in 12 sections stained with HE, PAS, Gomory and Giemsa methods. The epidermis was uneven and atrophic, with focal irregular elongations and anastomoses with diffuse hyperkeratoses. Slight chronic inflammatory infiltrate with enlarged number of mast cells was found perivascularly in the papilar dermis. Skin adnexa were missing (Figures 3 and 4).

Histological and immunohistochemical test done in September/09 (methods used: HE, Giemsa, immunohistochemical: C-kit): The skin sample revealed a slight ortokeratotic hyperkeratosis, as well as moderate acanthosis with a mild epidermal atrophy and spongiosis. There were dermal edema and moderate perivascular infiltrations of lymphocytes and oval and spindle-shaped cells (CD117+, CD1-). Giemsa staining focally revealed granules within those cells, which undoubtedly indicated mast cells (Figure 4).

Control HIV RNA PCR test: in January/2011 was still negative in the patient's blood.

Control blood CD4 counts: were decreased during the 2009-2011 period: in October/09 and January/11 levels were 198/ml and 237/ml, respectively (normally 600-1600/ml).
According to the WHO classification of mastocytosis, the following types of mastocytosis and mastocytosis syndromes were differentiated: 1. cutaneous mastocytosis (e.g. urticaria pigmentosa) involving only the skin with excellent prognosis in children, tends to regress spontaneously during adolescence; 2. systemic mastocytosis: mostly affecting more than one organ, without documented cases of spontaneous remission, it exists in several forms: a. indolent systemic mastocytosis, usually occurs with skin changes that are similar to those of urticaria pigmentosa, along with visceral organs involvement with relatively mature mast cells, with absence of hematological abnormalities and signs of progressive damage to internal organs, this form is associated with an almost normal life expectancy; b. aggressive systemic mastocytosis, characterised by progressive infiltration of mast cells which often exhibit cellular atypia into different organs, hematologic abnormalities and splenomegaly are common, while appearance of skin lesions is rare (10%), the prognosis is poor; c. systemic mastocytosis with chronic myelomonocytic leukemia (SM-CMML), characterized by over 10% atypical mast cells in peripheral circulation and diffuse bone marrow infiltration. The disease has a rapid fatal course (3, 4). Due to the suspicion of indolent systemic mastocytosis, the following procedures were repeated in our patient: Doppler portal vein US (which excluded thrombosis); computed tomography and abdominal nuclear magnetic resonance imaging; DEXA-scan – recommended by a hematologist due to elevated alkaline phosphatase levels; bone marrow biopsy. Repeated liver and bone marrow biopsy showed normal count of mast cells, so systemic mastocytosis was excluded as well as the need for interferon therapy.

In differential diagnosis systemic mastocytosis is often mistaken for other lymphoreticular diseases, hairy cell leukemia and histiocytic proliferation due to mast cells granules that may be hard to notice in routine histological sections. The main indication for their identification is the presence of nests of cells that “resemble monocytes” associated with eosinophilia and sclerosis. The systemic mastocytosis diagnosis is than easily confirmed by Giemsa stain method (purple granules), toluidine stain method (metachromatic granules), chloroacetate esterase stain method (bright red granules, with positive granulocytes). Tryptase
immunostaining method is more sensitive than histochemical staining technique for confirming the presence of mast cell differentiation. CD117/c-kit, which shows cell membrane immunoreactivity, also promises to be a sensitive marker (1, 10-13). In our case the diagnosis of urticaria pigmentosa was also confirmed by immunohistochemical findings of numerous spindle-shaped and oval cells (CD117+ and CD1a-) present in the dermis. Immunohistochemical finding of mastocytosis is based on the presence of antigen CD117+ on the surface of mast cells (11, 12).

In terms of the aforementioned, systemic mastocytosis is characterised by abnormal mast cell infiltration of the spleen, lymph nodes, bone marrow and liver, with or without skin involvement. There is a predominance of middle-aged male patients, approximately 60 years of age. Patients suffer from skin changes, anaphylaxis, pain and/or bone fractures (osteoporosis, osteolytic changes, osteosclerosis, or mixed), gastrointestinal symptoms (abdominal pain, diarrhea and peptic ulcer), respiratory difficulties (wheezing, dyspnea), hematological changes (cytopenia, eosinophilia, monocytosis, mast cells in blood circulation) or hepatosplenomegaly. Many of these symptoms are related to the release of histamine from mast cells. Therefore, a third-generation antihistamine was introduced into the therapy of our patient.

Absence of skin changes, presence of cellular atypia, and association with hematological diseases are unfavorable prognostic factors. (1, 10, 11). There are reports on rare association of systemic mastocytosis with mediastinal germ cell tumors (3, 4).

According to several authors, although there are no specific reports on the interaction of human immunodeficiency virus (HIV) and mast cells in AIDS patients, there is an interaction with basophilic granulocytes which are also FcεR1α (α subunit of the human high-affinity IgE receptor) - carriers like mast cells. Firstly, HIV transactivator protein (Tat) acts as a specific chemoattractant for FcεR1α-positive cells through its interaction with the CCR3 chemokine receptor (type 3 – protein encoded by CCR3 gene, recently designated as CD193) (13); Secondly, peptides derived from HIV such as HIV-1 envelope gp41 peptides are chemotactic for basophilic granulocytes (14), and finally, basophils show wide HIV receptor surface expression, such as CD4, CCR3, CCR5 (chemokine receptor type 5 – protein encoded by CCR5 gene, recently designated as CD195) and CXCR4 (chemokine receptor type 4 – protein encoded by CXCR4 gene, recently designated CD 184) (15), which, together with HIV Tat protein, can upregulate CCR3 (13). Although there is evidence of HIV infected basophilic granulocytes, the presence of similar analogy between HIV and mast cells remains unclear (9, 13, 16). Nevertheless, recent data provided in vivo, showed that in infected persons during HAART, tissue mast cells, raised from infected circulating progenitor mast cells, represent a long-lived reservoir of persistent HIV (17).

Conclusion
We present a case of mastocytosis in an AIDS patient as a third case published in world literature, in order to underline the possibility of development of cutaneous mastocytosis in persons with AIDS, due to immunogenetic damage and possible immunogenetic rearrangements.

Abbreviations
AIDS - Acquired immunodeficiency syndrome
HIV - Human immunodeficiency virus
HAART - Highly active antiretroviral therapy
ddi - Didanosine
3TC - Amivudine
EFV - Efavirenz
RNA - Ribonucleic acid
PCR - Polymerase chain reaction
WBC - White blood count
ALT - Alanine aminotransferase
AST - Aspartate aminotransferase
PT - Prothrombin time
APTT - Activated partial thromboplastin time
ANA - Antinuclear antibodies
ANCA - Antineutrophil cytoplasmic antibodies
Hep-2 cells.- Cells derived from a human laryngeal epithelial cell line
US - Ultrasound
DEXA - Dual-energy X-ray absorptiometry
WHO - World Health Organization
SM-CMML - Systemic Mastocytosis with Chronic Myelomonocytic Leukemia
Tat - HIV transactivator protein
References

Diskusija: Dijagnoza utrkarije pigmentoza je kod bolesnika postavljena na osnovu anamneze, kliničke slike, relevantnih laboratorijskih nalaza (značajno povišene vrednosti ukupnih IgE u serumu i povišene vrednosti 5-hidroksi-indol-sirćetne kiseline u 24-časovnom urinu) i histološkim pregledom (specifično bojenje) biopsije kožnih promena i, posebno, imunohistohemskim nalazom prisustva brojnih vretenastih i ovalnih ćelija u dermisu koje su CD117+ i CD1a+. Kod našeg bolesnika pronađeni su i oštećenja jeter, hronični holecistitisa, leukopenija, trombocitopenija i eozinofilija (relativna) koji su u jednom momentu pobođivali ozbiljnu sumnju na sistemsku mastocitozu. Sistemska mastocitoza se karakteriše progresivnom infiltracijom različitih organa mast ćelijama koje često ispoljavaju ćelijsku atipiju. Hematološke abnormalnosti i splenomegali je uobičajene. Iz ovih razloga rađene su višestruke biopsije jeter i kostne srži, kao i CT i MR pregled jeter i abdomena. Kako ovi pregledi i metode nisu mogle potvrditi prisustvo mast ćelija u većem broju, došlo je do zaključka da u ovom momentu nema elemenata za dijagnozu sistemskih bolesti. Biopsija jeter je otkrila samo blag oblik hroničnog persistentnog hepatitisa sa fibrozom.

Prema podacima iz literature, kod obolelih od AIDS-a utvrđena je interakcija između virusa i bazofilnih granulocita: HIV transaktivacioni protein (Tat) predstavlja specifični hemotaktrant za ćelije koje na svojoj površini poseduju receptore visokog afiniteta za vezivanje imunoglobulina klase E (FceRIα, pozitivne ćelije), hemotaksija se ovdija uz pomoć hemokinske...
receptora tip 3 (CCR3); peptidi u sastavu virusnog glikoproteina gp41 – HIV gp41 predstavljaju hemoatratante za bazofilne granulocite; na svojoj površini, bazofilni granulociti poseduju HIV receptore (CD4, CCR3, CCR5, CXCR4) koji zajedno sa HIV-Tat proteinom povećavaju ekspresiju CCR3. Ipak, za sada nedostaju publikovani radovi o interakciji između virusa humane imunodeficijencije (HIV) i mast ćelija (koji takođe na svojoj površini nose isti receptor \( FcεRI \), kao i bazofili).

Zaključak: Prikazani slučaj ne predstavlja samo treći do sada u svetu publikovan slučaj mastocitoze kod bolesnika sa AIDS-om, nego, ukazuje i na potrebu za daljim ispitivanjem moguće patogenetske uloge imunogenetskih oštećenja i imunogenetskih rearanžmana kod obolelih od AIDS-a.

Ključne reči

Urticaria Pigmentosa; HIV; Sindrom stečene imunodeficijencije; Komorbiditet