INTERNAL DISEASES

UDC 616.72-002.77+616.16-007.64-079.4

Rheumatoid arthritis associated with Rendu — Osler — Weber disease: Second description*

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For citation: Carvalho J. F. de, Maia Rodrigues C. E., Freitas Zerbini C. A. de, Churilov L. P. Rheumatoid arthritis associated with Rendu — Osler — Weber disease: Second description. *Vestnik of Saint Petersburg University. Medicine*, 2021, vol. 16, issue 3, pp. 147–152.
https://doi.org/10.21638/spbu11.2021.301

The article presents second ever published description of rheumatoid arthritis case co-morbid with Rendu — Osler — Weber disease (hereditary hemorrhagic teleangiectasia) in a 63-years-old female patient. The aim is describing the first case report of a patient who after a confirmed hereditary hemorrhagic teleangiectasia diagnosis developed rheumatoid arthritis one year later. Historical data and brief pathophysiological characteristic of both diseases and their possible intermingle are included: (i) mutant genes in hereditary hemorrhagic teleangiectasia all encode proteins involved in the TGF-beta signaling pathway, and increased plasma levels of TGF-beta-1 and vascular endothelial growth factor have been seen in such patients; (ii) TGF-beta plays a role in the development of synovial cell proliferation, inflammation, and angiogenesis in rheumatoid arthritis; (iii) TGF-β regulates thymic T-cell selection, inhibits cytotoxic T lymphocyte (CTL), Th1-, and Th2-cell differentiation while promoting peripheral

* Contribution of L. P. Churilov was supported by the grant of the Government of Russian Federation for state support of scientific research carried out under the supervision of leading scientists, agreement 14.W03.31.0009.

Treg-, Th17-, Th9-, and Tfh-cell generation, and T-cell tissue residence in response to immune challenges, all essential for pathogenesis of rheumatoid arthriitis. The defect in its reception as well as its compensatory increased blood content theoretically can alter autoimmunity thus facilitating in Rendu — Osler — Weber disease patients the development of systemic autoimmune diseases.

Keywords: rheumatoid arthritis, Rendu — Osler — Weber disease, hereditary hemorrhagic telangiectasia.

Introduction

Rheumatoid arthritis (RA) is the most common systemic autoimmune rheumatic disease, occurring in 0.5 to 1 % of the population [1]. It is characterized by polyarticular involvement, which mainly affects the peripheral joints and can lead to major deformities. There are extra-articular manifestations described in this illness, such as secondary Sjögren's syndrome, rheumatoid vasculitis, amyloidosis, pleuritis and others [2]. It has been first medically described in Europe in 1800 by a French physician Augustin Jacob Landré-Beauvais (1772–1840). Paleopathological data from Americas witnessed for existence of RA among ancient rooted population of New World, but similar data are absent or doubtful for the ancient bones of the Old World, hence there is an assumption that RA was imported from Americas to Old World with some unknown antigens/pathogens and habit of smoking not earlier that in late XV — early XVI centuries [3].

Rendu — Osler — Weber disease (ROW) or hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder with varying penetrance and expression. The genetic mutations identified for the majority of ROW cases alter the expression of receptor proteins [endoglin (ENG) and activin receptor-like kinase 1 (Alk-1)], both involved in transmission of signals from transforming growth factor-beta 1 and/or 3 (TGFβ-1,3). The last two autacoids control the growth and functions of endothelial cells during angiogenesis [4]. For the first time ROW was differentiated from hemophilia and described in details as a distinct entity by French physician Henri Jules Louis Marie Rendu (1844–1902), although several cases of the illness were reported earlier in Britain [5]. The essential contribution from the Canadian-American physician William Bart Osler (1849–1919) was a series of cases with first postulation of the familiar nature of disease [6]. A bit later British physician Frederick Parkes Weber (1863–1962) amplified its clinical description [7]. The disease belongs to vasopathias and is characterized by hemorrhagic syndrome with diffuse telangiectasias mainly on the face and hands, and may also be present as arteriovenous fistulas in organs, such as the brain, liver and intestine. Sometimes lung vessels are involved with pulmonary hypertension. It does not have a specific treatment. The diagnosis is made by characteristic signs and symptoms: facial telangiectasia with involvement of hands or oral cavity; recurrent epistaxis; arteriovenous malformations with visceral involvement; and a positive family history. Diagnosis is confirmed upon the presence of at least three of these manifestations. Intestinal involvement may be aggravated by adenomas and even adenocarcinomas [4; 8]. A patient with RA associated with ROW was previously described in the literature only once [9].

So, this article aimed on describing the first case report of a patient that after a confirmed diagnosis of ROW developed RA one year later.

Case description

A 63-years-old female patient was diagnosed with intestinal mucinous adenocarcinoma in 2008. She was submitted to intestinal and regional lymph node resections and also treated with 6 cycles of chemotherapy with oxaliplatin and fluoracil. These drugs were interrupted due to liver toxicity, and the liver biopsy was compatible with vaso-occlusive disease. At the time, she evolved with several recurrent episodes of intestinal bleeding and started episodes of epistaxis, with normal platelet count. She underwent colonoscopy that revealed vascular ectasias, and received blood transfusions on 10 different occasions. Hemostasis was performed with argon laser (2 sessions). The angiotomography of the abdomen revealed an enlarged liver with an increased caliber of the hepatic artery. There was a spiral aspect of its intrahepatic branches with associated arteriovenous fistulas visualized throughout the parenchyma and some areas with small nodules. An enlarged portal vein was also detected. The cerebral angiotomography ruled out involvement of brain vessels. Pulmonary angiotomography showed arteriovenous fistula in the upper lingual region. This area was embolized in 2017, evolving after one week to a pulmonary infarction. Dermatoscopy revealed telangiectasias on her fingers, tongue and lips (Figure *a, b*). She had a family history of epistaxis in his father and two brothers, one of them with hemoptysis and diagnosis of pulmonary arteriovenous fistula. The HHT disease-associated gene testing was positive for heterozygosis state for the c1330–31dupGT germ line mutation in exon 9 of the Alk-1 gene. The patient fulfilled the diagnosis criteria for ROW [4; 8], in fact, she had recurrent epistaxis, telangiectasias in her face, hands and oral cavity; arteriovenous malformations on her lungs; and a positive family history. Her adenocarcinoma also maybe mechanistically related to ROW with intestinal involvement. She evolved well, without further episodes of intestinal bleeding, maintaining mild episodes of epistaxis.

But in 2013, she sought a private clinic with polyarthritis and diffuse joint pain initiated in 2009. On examination, she had polyarthritis including wrists, all metacarpal-phalangeal and proximal interphalangeal joints, in addition to knees and ankles, associated with morning stiffness which lasts 60 minutes. The laboratory tests revealed: anti-citrullinated protein antibody 130 IU/mL and rheumatoid factor 445 U/mL, erythrocyte sedimenta-

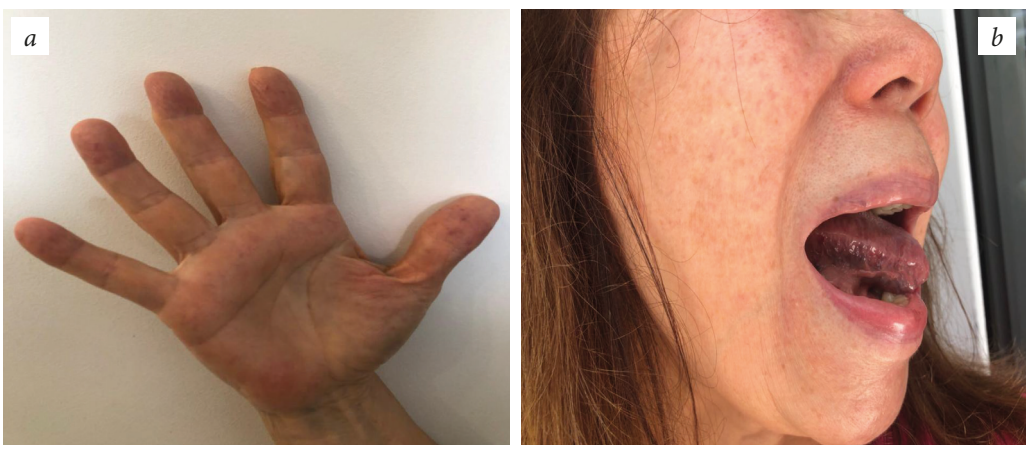

Figure. Photographs from the patient showing telangiectasias on her (*a*) fingers and hand, and (*b*) on her tongue and lips

tion rate 108 mm/hour and C-reactive protein of 22 mg/dL. A diagnosis of rheumatoid arthritis was performed. Due to the anamnesis of neoplastic, liver and gastrointestinal alterations, treatment with rituximab 1g was chosen and repeated after 15 days, and subsequently administered each 6 months. Purified protein derivative skin test for tuberculosis was negative and chest X-ray was normal. The patient received 12 cycles (2 applications each 6 months) and achieved a complete clinical remission, without signs of arthritis and with C-reactive protein level <0.05 mg/dL. Currently, she stays on maintenance of rituximab and on vitamin D 1,000 IU/day, melatonin 3 mg for insomnia, omega-3 unsaturated fatty acids 1g, as well as probiotics and others vitamin supplements. Sporadically, it presents mild epistaxis, without any episode of gastrointestinal or pulmonary bleeding.

Discussion

A case report describing a patient with glucocorticoid-induced ROW was found in the literature [10]. But this is distinct from the case of our patient since in her ROW appeared before the diagnosis of RA and the patient had no previous chronic condition for which she could use corticosteroids for a long term.

Regarding joint involvement in ROW, only cases of septic arthritis, algodystrophy of the upper extremity and pseudo-hemarthrosis were described. In fact, vascular telangiectasis in joints may favor the interference of microorganisms and bleeding [11–13]. Reinforcing this findings, a study observed the need for hospital admittance in a group of 73 ROW patients and 219 matched controls during a 20 years follow-up period and concluded that ROW patients had an increased probability of infections in joints and bones and of bleeding episodes. However, the incidence of thromboembolisms, cerebral abscesses and other conditions commonly considered to be related to ROW was comparable between the patients and the controls [14].

Interestingly, there is a description of ROW in other rheumatic diseases, such as Sjogren's syndrome, primary biliary cirrhosis, and scleroderma [15]. Telangiectasias may also be present in the limited form of scleroderma, but the clinical symptoms and other signs of this disease make its differential diagnosis with ROW very easy. It is possible that one of the pathophysiological mechanisms of telangiectasia — both in the limited form of scleroderma and ROW may involve ENG, a glycoprotein that makes up endothelial nitric oxide, which has been found to be altered in patients with scleroderma [16]. Furthermore, some possible pathogenetic explanations of the HHT and RA association might be:

— HHT mutant genes all encode proteins involved in the TGF-beta signaling pathway, and increased plasma levels of TGF-beta-1 and vascular endothelial growth factor have been seen in HHT patients [4];
— TGF-beta plays a role in the development of synovial cell proliferation, inflammation, and angiogenesis in RA.
— TGF-β regulates thymic T-cell selection, inhibits cytotoxic T lymphocyte (CTL), Th1-, and Th2-cell differentiation while promoting peripheral Treg-, Th17-, Th9-, and Tfh-cell generation, and T-cell tissue residence in response to immune challenges [17].

The defect in its reception as well as its compensatory increased blood content theoretically can alter autoimmunity thus facilitating in ROW patients the development of systemic autoimmune diseases.

Could targeting TGF-β-signaling then be a treatment strategy for both conditions? Future studies are desired in this field.

In conclusion, this is the second description in the literature of a patient with ROW disease who presented RA, after one year of evolution.

Ethical statement

The authors declare that they followed the World Medical Association Declaration of Helsinki in this study. An informed consent was obtained from the patient for publication of the case. Images used do not uncover a personality of patient.

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Received: March 8, 2021
Accepted: September 30, 2021

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