POLISH ARCHIVES OF
Internal Medicine
POLSKIE ARCHIWUM MEDYCYNY WEWNĘTRZNEJ

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Article type: Clinical image

Received: March 27, 2024.

Revision accepted: April 23, 2024.

Published online: April 25, 2024.

ISSN: 1897-9483

Pol Arch Intern Med.

doi:10.20452/pamw.16744

An advanced case of Waldenström's macroglobulinemia complicated by acquired hemophilia a in a patient with neurofibromatosis type 1

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A 52-year-old female patient with a history of Recklinghausen's disease (Neurofibromatosis type I (NF-1)) was admitted to the Hematology Department from a regional hospital after a spontaneous rupture of the right brachial artery (previously surgically treated) with suspected

Waldenström's macroglobulinemia. Upon admission, laboratory tests revealed normocytic anemia (Hb 7.7g/dl; reference range, 12.0–16.0 g/dl), leukopenia (white blood cells 2.28 x 10^9/L; reference range, 4.00 x10^9/L–10.00 x 10^9/L), and thrombocytopenia (platelets 35 x 10^9/L; reference range 130 x 10^9/L–400 x 10^9/L) activated partial thromboplastin time (aPTT) prolonged to 101.4 seconds (reference range 25.1–37.7s), hypofibrinogenemia (fibrinogen 102 mg/dl; reference range 170.0– 420.0 mg/dl), elevated levels of C-reactive protein (388 mg/l; reference range 0.00–5.00 mg/dl), beta-2-microglobulin, and total protein. The total concentration of immunoglobulin M (IgM) was 2560 mg/dl (reference range 40.0–240.0 mg/dl), and immunofixation confirmed the monoclonality of the IgM kappa class monoclonal protein. The bone marrow aspirate showed an increased number of lymphocytes (30.4%; reference range 3.0–18.0%) with a pathological phenotype in flow cytometry: CD19+CD38+light chain kappa+. Failure of a correction on aPTT mixing study prompted further evaluation of individual clotting factors. There was a profound decrease in factor VIII activity (<1%; reference range 70– 150%). A Bethesda titer for factor VIII antibody was completed and found to be significantly elevated (180 Bethesda Units [BU]).

In the abdominal computed tomography (CT), an enlargement of the liver (19 cm) and spleen (22.5 cm) was demonstrated. Waldenström's macroglobulinemia (WM) also known as lymphoplasmocytic lymphoma was diagnosed (International Prognostic Scoring System for Waldenstrom Macroglobulinemia - IPSSWM intermediate)

with concomitant acquired hemophilia A (AHA). Initially, the patient was administered a 4-day pulse therapy with intravenous (i.v.) dexamethasone (20 mg per day). As WM treatment five treatment cycles with bortezomib, dexamethasone and rituximab protocole (BDR) were scheduled. In the initial 21-day cycle, bortezomib was given subcutaneously (s.c.) at 1.3 mg/m^2 on days 1, 4, 8, and 11. For cycles 2 through 5, bortezomib was administered s.c. at a weekly dose of 1.6 mg/m^2 on days 1, 8, 15, and 22 across four consecutive 35-day cycles.

Additionally, during cycles 2 and 5, the patient received IV dexamethasone at 40 mg and IV rituximab at 375 mg/m^2 on days 1, 8, 15, and 22, totaling eight infusions of rituximab. 48 hours after completing the first BDR cycle, the patient reported severe abdominal pain in the upper left quadrant. Physical examination revealed abdominal wall rigidity and tenderness in that area. Subsequent tests showed a decrease in hemoglobin from 9.3 mg/dl to 6.7 mg/dl. Abdominal computer tomography (CT) revealed a significant amount of fluid in the peritoneal cavity suggesting active bleeding - an oval fluid collection approximately 15.0 cm x 8.2 cm x 13.5 cm adjacent to the spleen (Figure 1A). Additionally, the CT scan showed a dissection of the abdominal aorta wall extending to the right common iliac artery over a length of about 7.2 cm without signs of active bleeding (Figure 1B). After the patient was qualified for urgent laparotomy, supplementation with recombinant coagulation factor VII (Novoseven® 5mg i.v. every 2 hours) was initiated. During the surgery, bleeding from the splenic artery was identified, and a splenectomy was performed. In the histopathological examination of the spleen, a solid infiltrate of clonal Ig Kappa (+) plasma cells and a few PAX5 (+), CD20+ B lymphoid cells were demonstrated, consistent with the previously diagnosed lymphoplasmocytic lymphoma. In the following weeks, treatment was continued according to the BDR protocol, achieving gradual normalization of blood and bone marrow morphology, factor VIII activity, aPTT, and serum IgM levels. The patient completed treatment 6 months ago. Currently, she is asymptomatic and remains under observation.

The literature has described cases of hemorrhagic complications in the course of WM associated with acquired hemophilia A (AHA) [1], as well as spontaneous dissections and ruptures of arteries in the course of NF-1 [2,3]. In the case described above, there was a development of secondary AHA in the course of WM in a patient with NF-1, where in the event of arterial rupture, the risk of life-threatening hemorrhagic complications was significantly increased. NF-1 is an autosomal dominant disorder with vascular abnormalities

as a well-recognized manifestation [4] and unlike WM and AHA cannot be effectively treated. A multicenter phase 2 trial confirmed high efficacy of the BDR protocol in the WM first line treatment, particularly for cases with low and intermediate IPSSWM [5] however this patient requires careful monitoring due to potential subsequent vascular complications in the course NF-1.

Article information

Acknowledgments None.

Funding None.

Conflict of interest None declared.

How to cite Dybko Z, Jodłowski G, Borkowski A, et al. An advanced case of Waldenström's macroglobulinemia complicated by acquired hemophilia a in a patient with neurofibromatosis type 1. Pol Arch Intern Med. 2024; XX: 16744. doi:10.20452/pamw.16744.

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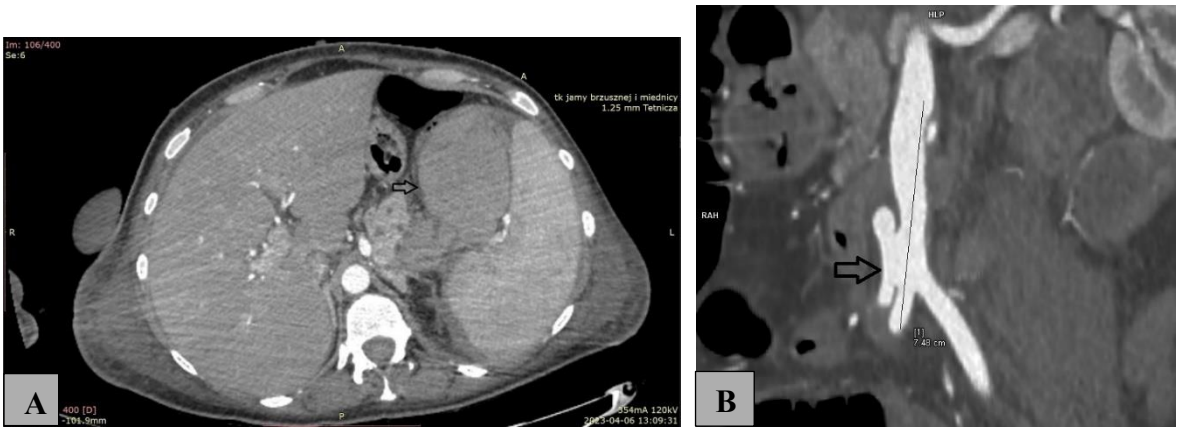

Figure 1 A – Computer tomography scan of the abdominal cavity: oval fluid collection approximately 15.0 cm x 8.2 cm x 13.5 cm adjacent to the spleen (black arrow); B – dissection of the abdominal aortic wall extending into the right common iliac artery over a length of approximately 7.2 cm without signs of active bleeding beyond the lumen of the vessels (black arrow)

Short title: A case of Waldenström's Macroglobulinemia and Acquired Hemophilia A