

Acquired Hemophilia A in a Patient with Non-Small Cell Lung Carcinoma: A Rare Paraneoplastic Phenomenon

Gal Ben Haim MD^{1*}, Uri Manor^{1,4*}, Sarit Appel MD², Shadan Lalezari MD³, Reuma Margalit-Yehuda MD¹ and Shmuel Steinlauf MD^{1,4}

Departments of ¹Internal Medicine C and ²Radiation Oncology, and ³National Hemophilia Center and Thrombosis Unit, Sheba Medical Center, Tel Hashomer, Israel

⁴Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

KEY WORDS: acquired hemophilia, non-small cell lung carcinoma (NSCLC), malignancy, factor VIII, paraneoplastic syndrome

IMAJ 2017; 19: 128–130

Hemophilia A is defined as a deficiency in clotting factor VIII. Although usually a congenital disease, an acquired variant known as acquired hemophilia A (AHA) can also be diagnosed. AHA is a rare bleeding disorder, with an approximate incidence of 1 per million per year, usually affecting the elderly. It is associated with underlying conditions such as autoimmune diseases, the post-partum period, malignancies, and more. In AHA, endogenous factor VIII is inhibited by circulating autoantibodies. Consequently, patients manifest with bleeding in a pattern interestingly different from the congenital disease: hemarthroses are rarely seen, and instead, hemorrhages of the skin, mucous membranes, muscles and soft tissues occur. Specifically, gastrointestinal and urological bleeding is common. The bleeding may be lethal, requiring immediate hemodynamic support.

Diagnosis of AHA requires a high grade of suspicion, as patients without hematologic histories may present to physicians of various specialties with signs and symptoms most likely attributable to other diseases. A patient without a known coagulopathy presenting with prolonged activated partial thromboplastin time (aPTT), normal prothrombin time (PT) and a suggestive clinical picture, should raise the suspicion of acquired hemophilia. Tests for coagula-

tion factor levels should ensue, with isolated low levels of factor VIII implying AHA. Additional tests include timed plasma mixing tests to differentiate between factor deficiency and an inhibitory substance, the Bethesda assay for inhibitor titer quantification, and a test for the lupus anticoagulant (LAC). Treatment of AHA consists of two major efforts: inhibitor eradication and hemostatic therapy. If an underlying morbidity (namely, a malignancy) is suspected as the trigger, and the patient's situation permits, specific treatment is advised [1].

We report a 75 year old patient who presented with lower gastrointestinal bleeding and life-threatening hematuria. Workup disclosed AHA and poorly differentiated non-small cell lung carcinoma (NSCLC), for which he received hemodynamic support, factor replacement, immunosuppression and radiotherapy. This effort led to early resolution of the hemophilia.

PATIENT DESCRIPTION

A 75 year old male presented at the emergency department and was admitted to the hospital with urinary catheter obstruction, previously placed for benign prostatic hyperplasia (BPH)-related urinary retention. His pertinent recent medical history included unintentional weight loss and recurrent lower gastrointestinal bleeding (LGIB) in the previous several months. Following urinary catheter replacement, multiple blood clots were found to have caused the obstruction and he was hospitalized.

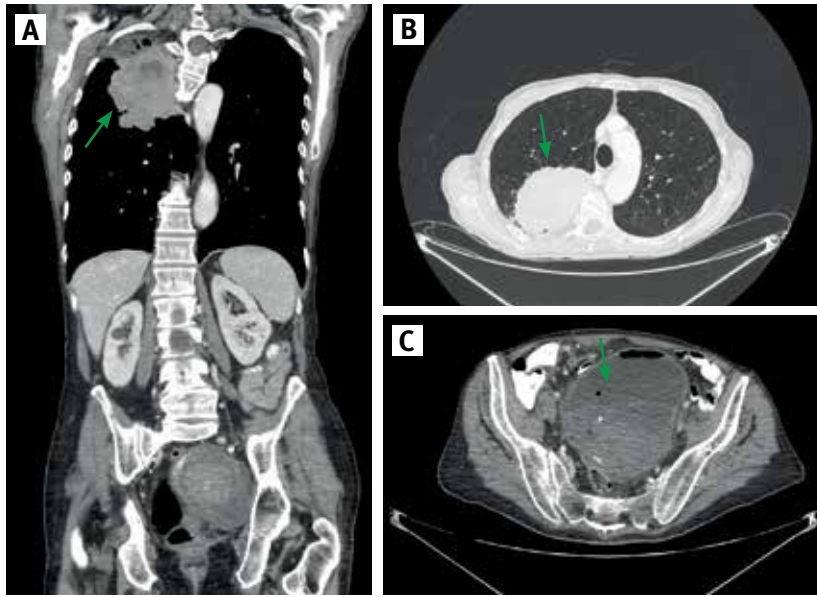
His medical history included heavy smoking, a congenital hypoplastic limb and BPH. Vital signs were unremarkable at admission, and a physical examination

was significant for cachexia and a new complaint of a painful lump in his right arm, that was confirmed by sonography as an intramuscular hematoma within the brachialis muscle. Laboratory workup revealed a severe hypochromic normocytic anemia (hemoglobin 7.82 g/dl) and a prolonged aPTT of 57 seconds. During the following days, the gross hematuria continued, leading to anemia refractory to aggressive blood transfusion. Therapeutic transurethral procedures failed to stop the hematuria, and pathologic sampling of the bladder and prostate demonstrated inflammation devoid of malignancy. Computed tomography (CT) unmasked a large right lung lesion, measuring 9 x 6 cm, adjacent to the chest wall, without hilar or mediastinal lymphadenopathy [Figure 1]. CT-guided core needle biopsy followed, disclosing carcinoma composed of pleomorphic large cells. Positron emission tomography (PET-CT) and brain magnetic resonance imaging (MRI) were performed, negative for viable metastases. An extensive coagulation workup was carried out, revealing a presumably new isolated factor VIII deficiency (< 1%, reference range 60–150) and evidence of factor VIII inhibitors on the Bethesda assay (20 Bethesda units, normal 0) with negative plasma mixing and LAC tests. The diagnosis was T3N0M0, stage IIB, poorly differentiated NSCLC, with concomitant acquired hemophilia A.

The patient's status deteriorated significantly. He was now bedridden, with hemoglobin and albumin levels reaching a nadir of 5.63 g/dl and 1.5 g/dl, respectively. He was treated simultaneously in three axes: hemostasis, immunosuppression, and treatment of the underlying disease. Hemostasis

*The first two authors contributed equally to this study

Figure 1. Patient's chest-abdomen-pelvis CT. **[A]** Coronal view, note lesion in right lung and bladder. **[B]** Axial view of lung lesion, measuring 9 cm in diameter. **[C]** Axial view of bladder, note indwelling catheter, air bubble, and tissue-like mass with calcifications (blood clot)



was maintained by infusions of packed red blood cells and recombinant factor VIII. Immunosuppression was started with intravenous methylprednisolone, and then switched to oral prednisone.

Regarding the tumor, surgery and chemotherapy were ruled out due to his poor medical condition and coagulopathy. Furthermore, tests negative for EGFR mutations precluded treatment with tyrosine kinase inhibitors. Hence, oncologic treatment was attempted with external beam radiation therapy (EBRT) – 2000 cGy in 5 fractions, targeted at the lung mass alone.

Three weeks since diagnosis and initiation of treatment, hemoglobin, aPTT and factor VIII levels had normalized independent of factor VIII and blood transfusions, and the patient was transferred to rehabilitation.

COMMENT

Our patient presented with large cell lung carcinoma, a tumor rarely associated with paraneoplastic syndromes in general and AHA in particular. Approximately 10% of AHA patients have an underlying malignancy, either hematologic (usually lympho-

proliferative) or solid. Studies characterizing solid tumors in AHA patients invariably describe the prostate as the leading site, along with lung, colon and pancreas among others. No correlation was found concerning extent or histology of the disease [2,3].

Is there a correlative relationship between the appearance of factor VIII inhibitors and cancer in this patient, or a causal one? A strong argument in favor of the latter is that although rare, this phenomenon has a strong temporal relationship with malignancies, thus rendering it a paraneoplastic syndrome. Immune associated paraneoplastic syndromes are attributable to cross-reactivity between the tumor and normal host tissues, due to antigenic similarity or immune modulation suppressing anti-self-reactivity. The exact pathogenesis in paraneoplastic AHA has yet to be discovered, but elements that appear to mediate breakdown of immune tolerance to factor VIII include age, characteristics of the tumor, environmental and genetic factors, such as human leucocyte antigen (HLA) class II DRB1 and DQB1 alleles and single nucleotide polymorphisms (SNPs) of the cytotoxic T lymphocyte antigen (CTLA) 4. Due to the probable dual role of the tumor

and the immune system in AHA, along with immunosuppression, which is the mainstay of the treatment, tumor-directed therapy (via surgery, chemotherapy, or radiation) is advised [1,2]. Our choice of treatment was based on this paradigm, namely corticosteroid immunosuppression and EBRT.

Prompt institution of an appropriate immunosuppressive treatment is crucial, yet the nature of the optimal regimen is unclear. Few randomized trials have been conducted due to impracticability, so management guidelines are predominantly based on case reports, retrospective cohorts and expert opinion. Furthermore, as AHA is primarily a disease of the elderly, treatment choice is complicated by considerations of concomitant diseases or triggering conditions. The backbone of immunosuppressive therapy is administration of corticosteroids, which are effective in achieving complete inhibitor eradication in 60–70% of patients with a median time to remission of approximately 5 weeks. Cyclophosphamide and other cytotoxic agents may enhance inhibitor eradication and prevent relapse; however, they are associated with severe adverse effects.

Recent years have brought increasing interest in the efficacy of the anti-CD20 antibody rituximab. Currently, there are no significant data supporting the superiority of rituximab over corticosteroids, and it is therefore recommended as second-line treatment. Extracorporeal removal of antibodies is also an acceptable means of eradication. This method is usually adopted when rapid inhibitor clearance is needed (e.g., pre-surgery), or as salvage therapy. Plasmapheresis or immunoadsorption protocols usually include standard immunosuppression with or without administration of intravenous immunoglobulin (IVIg). There is no rationale for giving IVIg as early-line monotherapy [1,4,5].

CONCLUSIONS

In addition to being a rare report of AHA in NSCLC, this case illustrates the importance of familiarity with the paraneoplastic AHA, and the spectrum of treatment it requires. In retrospect, our patient manifested with symptoms highly suggestive

of AHA: (i) significant unprovoked intramuscular, gastrointestinal and urinary bleeding; (ii) unexplained and persistent prolonged aPTT; and (iii) underlying malignancy, a condition assumed to trigger spontaneous activity of neutralizing autoantibodies against coagulation factor VIII. The treatment offered in this case is the epitome of interdisciplinary medicine: cooperation between experts in hematology, oncology, pathology, and radiology – all orchestrated by the internist. The rapid collaborative effort following the diagnosis

of AHA led to the early resolution of the coagulopathy, enabling stabilization of the patient and further treatment of his malignancy.

Correspondence

Dr. G. Ben Haim

Dept. of Internal Medicine C, Sheba Medical Center, Tel Hashomer 5265601, Israel

Phone: (972-3) 530-2464

email: galushbh@gmail.com

References

1. Shetty S, Bhavne M, Ghosh K. Acquired hemophilia A: diagnosis, aetiology, clinical spectrum and

treatment options [Review]. *Autoimmunity Rev* 2011; 10: 311-16.

2. Sallah S, Wan JY. Inhibitors against factor VIII in patients with cancer: analysis of 41 patients. *Cancer* 2001; 91 (6): 1067-74.
3. Hauser I, Lechner K. Solid tumors and factor VIII antibodies. *Thromb Haemost* 1999; 82 (3): 1005-7.
4. Collins P, Baudo F, Knoebl P, et al. Immunosuppression for acquired hemophilia A: results from the European acquired haemophilia registry (EACH2). *Blood* 2012; 120 (1): 47-55.
5. Huth-Kühne A, Baudo F, Collins P, et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. *Haematologica* 2009; 94 (4): 566-75.

“Remember, when the judgment’s weak, the prejudice is strong”

Kane O’Hara (1711-1782), Irish composer and playwright