Acquired Haemophilia in A Old Patient with Non Small Lung Cancer: A Case Report.

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Research Article

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Abstract

Acquired hemophilia A (AHA) is a rare autoimmune disease caused by autoantibodies against coagulation factor VIII and characterized by spontaneous hemorrhage in patients with no previous family or personal history of bleeding. We report here a case of AHA occured in the department of Medicina D'Urgenza in Sant'Andrea Hospital in a patinet with previous diagnosis of NSLC.

Introduction

Haemophilia A is definied as Factor VIII deficiency with a X-Linked trasmission; the genes are located on the X chromosome so hemophilia almost exclusively affects the male population, with outset in the pediatric age. The diagnosis can be found between 36 months in mild-moderate cases, up to one month in severe cases with factor VIII activity below 5%.

The nature of the clinical manifestations is substantially hemorrhagic such as hemarthrosis, retroperitoneal bleeding or muscle hematomas.

AHA (Acquired Hemophilia A), is a rare adulthood disorder with a similar clinical picture, with an incidence of 1 per 1 million per year, which essentially affects the elderly population[1].

Although the pathophysiological mechanism underlying this alteration is still being defined, the production of circulating autoantibodies inhibiting endogenous factor VIII seems to be involved[2, 3].

In about half of the cases AHA is idiopathic, but in a significant proportion it can be associated with neoplasia (11.8%), autoimmune diseases (13.4%), infection (3.8%) and pregnancy(8.4%).[4]

It has also been reported a case associated with SARS-cov 2 infection[5].

The main clinical manifestation of AHA is hemorrhage, present in more than 90% of patients at onset; the bleeding is spontaneous and severe in 70% of cases. The most common bleedings sites involved are subcutaneous tissue, followed by gastrointestinal haemorrhages, muscular haematomas, and less frequently genitourinary, retroperitoneal and even intracranial.

Hemarthrosis, which are typical manifestations of congenital haemophilia A, are rare in the acquired forms. Only in a minority of cases (only about 7%) AHA has not been associated with bleeding and is diagnosed while investigating for other pathologies or in view of an invasive procedure[4, 6].

AHA is considered a serious disease not only due to the incidence of severe bleeding but also due to the high mortality rate, estimated at over 10% in patients over 65 years[7].

According to the "International recommendations on the diagnosis and treatment of acquired hemophilia A" in order to make the diagnosis it is necessary to highlight an isolated lengthening of the aPT, normal

PT an isolated deficit of factor VIII; additional tests which are used in diagnostics include timed plasma mixing test, Lupus Anti-Coagulant (LAC) and Bethesda assay for inhibitor antibodies quantification [3].

In addition to treating the underlying cause such as oncological, autoimmune or infectious disease, the treatment of the disease includes immunosuppressive therapy and the use of recombinant activated factor VII or recombinant porcine factor VIII as a hemostatic drug[2, 8].

Case Description

We report the case of an 84 yearold patient with AHA who presented replenished bleeding in the muscle and liver tissue.

The patient was admitted in the Emergency Room of the “Sant’Andrea" hospital for acrocyanosis and algia of the right upper limb. He also reported dyspnea the week prior to emergency room access and denied any traumatic event to the affected limb.

He presented a pathological history of COPD, a pulmonary adenocarcinoma in the LID, which was already been treated with CHT and in a state of follow up by another hospital, hypertension, and previous IMA in 2018.

The home therapy included Ramipril, Cardioaspirin, Bisoprolol,Spironolactone, Pantoprazolo and Furosemide.

The patient reported having stopped Clopidogrel about 2 weeks before admission under the advice of his doctor, due to the appearance of a large hematoma on the affected limb.

Physical examination at the entrance: “Alert patient, oriented, pale skin, not sweaty, moderate hemodynamic compensation, right upper limb increased in volume, edematous, brachial and radial pulse not very detectable but present".

Vital signs BP 100/60, HR 90, SpO2 99%.

Hematochemical tests were then performed which documented a normocytic normochromic anemia, HB 7.2 g / dl, RBC 2.5, PLT 263,000, WBC 7.090 with appropriate formula, liver and kidney functions in normal range, INR 1.08, aPTT 2.24, D-Dimer 2856 .

During the period in the emergency room a transfusion with 1U of concentrated red blood cells was administered and requested a chest and upper limb Angio-CT which documented:

"... Is reported the presence of a volumetric increase in the right arm, compared to the contralateral one, due to the presence of ablood collection in the context of the biceps muscle in the perihumeral site…After mdc is observed a blood spreading of mdc as for bleeding in the active phase.

Collaterally to the VII hepatic segment area of focal hypodensity of 3.5cm in which context blood spreading is observed as for bleeding in the active phase. "

An upper limb arteriography was therefore performed and a superselective catheterization, with subsequent embolization.

Despite the procedure, the patient continued to have variability in his hemoglobin and coagulation values.

After that the patient was admitted to the “Medicina d’Urgenza “ department: blood chemistry tests were repeated which confirmed the presence of hemoglobin values of 7.1 g / dl despitetransfusion support, normal liver and kidney function, normal inflammation indices, INR 1.07, aPTT 2.51 (VN 0.8- 1.2) 79sec.

From an interview with the patient and with his son we learned that in the preceding months the patient had made 4 admissions to different hospitals for episodes of acute anemia, without mention of any trauma.

It was decided to carry out a new transfusion and a thorough coagulation screen was performed, showing an isolated factor VIII deficiency (0.7%, reference range 50-150).

At the time of diagnosis, the patient decided to resign against medical advice, giving up therapy, relying on home palliative care.

Tab.1 Coagulation parameters of the patient.

PT **Normal range** **0.9-1.2** **70-120%** **10-13sec**	**1.16** **79%** **13.9sec**
aPTT n.r. 25-35sec 08-1.2	**74 sec** **2.36 ratio**
D-Dimer nr < 243	**5498 ng/ml**
Fibrinogen n.r 200-400	446 mg/ml
Factor VIII Nr 50-150%	**0.7%**
Factor IX 65-150%	89%

Discussion

AHA represents a very rare and potentially lethal disease which, unlike Hemophilia A, usually arises in adulthood.

This pathology requires a multidiscilpinar approach that involves experts in internal medicine, hematologists, urgent specialists, immunologists, radiologists and laboratory doctors.

The importance of diagnosis, and in particular of early diagnosis, is underlined by the high mortality rate of patients suffering from this condition, as the probability of severe bleeding concerns 70% of these patients.

The diagnosis, as mentioned, starts from the suspicion of prolonged aPTT in the absence of a known Coagulopathy, therapy with heparin e.v. and LAC negative, confirmed by the dosage of coagulation factors, with evidence of FVIII deficiency.

Therapy, as mentioned, can be aimed at turning off the immune stimulus that leads to the production of anti-FVIII antibodies, through the use of therapies such as Corticosteroids associated with

cyclophosphamide, or according to more recent studies with monoclonal autoantibodies such as rituxiamb (anti CD20).

Another interesting therapeutic approach, which we can define as hemostatic and that concerns approximately 70% of patients with AHA, involves the use of FVIIa or activated prothrombin complex concentrate or Recombinant porcine factor VIII. [2, 3, 4]

Given the specialistic nature of this treatment, it is advisable to contact centers specialized in the treatment of haemophilia.

In order to arrive at the diagnosis and right therapy, it will therefore be important to compare the patient's clinic, the laboratory and anamnestic data.

The diagnostic challenge consists in the multidisciplinar approach, in the polypharmacy and polypathology typical of the elderly population that can mask the clinical picture, and also from the rarety that causes the poor knowledge and consequently the underdiagnosis.

In conclusion AHA is likely an underdiagnosed pathology, and though in about half of the cases is idiopathic, in a significant proportion it can be associated with neoplasia, autoimmune diseases, infection. Consequently it’s advisable to exclude this pathology in these conditions, especially in the elderly population which can mask symptomatology.

Declarations

Fundings: N.A.

Conflicts of interest: The authors declare that they have no conflict of interest.

Consent to partecipate/for publication: Written informed consent was obtained by patient for publication of this case.

Authors' contributions: Dr. Dulcetti participated in article preparation.

All authors materially participated in the research.

All authors participated in data collection.

All authors have approved the final article

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Figures

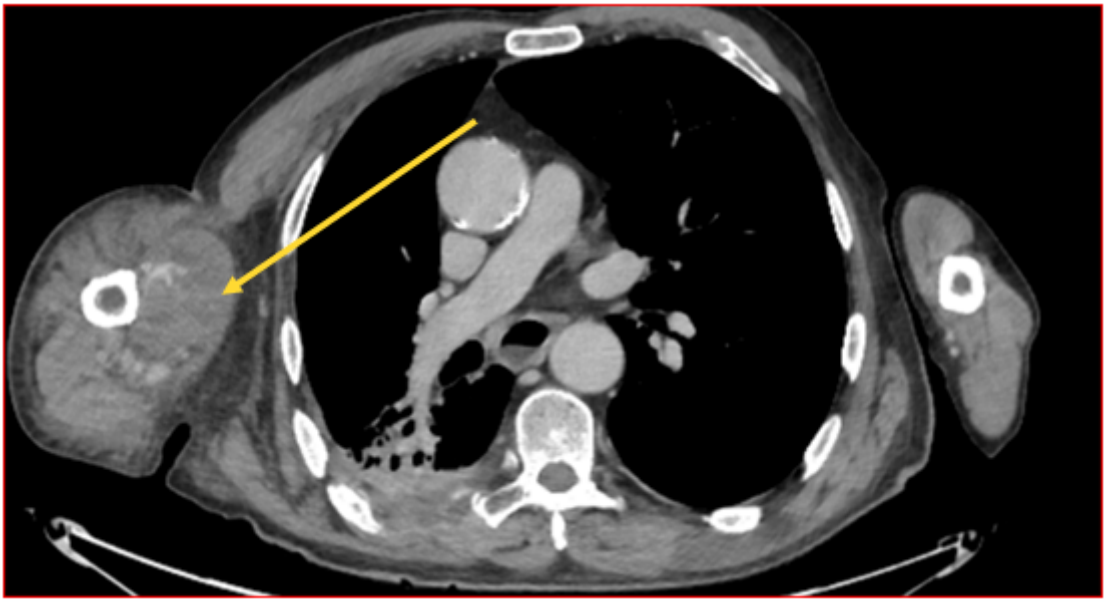

Figure 1

CT showing an Hematoma of the right upper limb.

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