Cold autoimmune hemolytic anemia: a rare association with triple-positive breast cancer

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ABSTRACT
A 45-year-old Asian woman was presented with fever, easy fatigability, shortness of breath, cervical and axillary lymphadenopathy and other signs and symptoms of anemia. After all the baseline work-up, the patient was investigated for Mono-coombs C3d levels, which were elevated, suggesting the diagnosis of Cold autoimmune hemolytic anemia (Cold AIHA). An Ultrasound-guided true-cut biopsy was done to determine the primary cause associated with it, which showed the presence of tumor cells arranged in cords and clusters. They have dark staining cells with mitotic activity, suggestive of breast carcinoma as an association of Cold AIHA. Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) were sent, which came out to be positive. So, the patient was diagnosed with Cold AIHA in association with triple-positive breast cancer.

1. Introduction
Cold Autoimmune Hemolytic Anemia is a disease caused by an increase in the level of cold-reactive antibodies. Mostly, it is associated with any secondary cause, like lymphoproliferative disorders, autoimmune diseases, and infectious causes. Rarely, it is associated with the use of drugs and solid malignancies including breast cancer. It usually presents with signs of anemia, jaundice, reticulocytosis, increases in total bilirubin and positive Direct Antiglobulin Test (DAT). The definitive diagnosis is made in the presence of mono-specific C3d levels. Steroids are the cornerstone treatment for Cold AIHA, but managing the primary cause is the definitive remedy.

2. Case presentation
A 45-year-old Asian woman with past medical history of diabetes mellitus, hypertension and a positive family history of Chronic Myeloid Leukemia (CML) in the first-degree relative presented to us with complaints of fever, lethargy, cough (aggravated with cold temperature exposure) and shortness of breath. The patient had symptoms of low energy which affected her daily living activities, associated with easy fatigability. She denied syncpe, easy bruising, yellowish discoloration of eyes and skin, night sweats, shortness of breath on lying flat or at night or any other active complaints. Initially, the patient was given ceftriaxone, azithromycin, vitamin B12, and iron supplements as an empiric treatment for fever, cough and easy fatigability.

The physical examination was unremarkable except for severe pallor, lymphadenopathy in two pectoral groups of lymph nodes and the use of accessory muscles while breathing. The laboratory findings were as follows: Hemoglobin: 4.49g/dL, MCV: 80fL, total leucocyte count: 18,000 white blood cells per microliter, serum total bilirubin of 2.63μmol/L with direct bilirubin of 1.30μmol/L, reticulocyte count: 1.05%, LDH: 5184 U/L, while rest of the labs were within normal limits. Her red cell antibody screening, monospecific coombs C3d came out to be positive with positive direct coombs test which showed resolving the pattern of red cell agglutination after incubation at 37°C, confirming the diagnosis of Cold AIHA. The differential considerations included Non-Hodgkin lymphoma, Chronic Lymphocytic Leukemia (CLL), HIV and any systemic malignancy leading to the development of cold AIHA. Computed Tomography scan of neck, chest, abdomen, and pelvis was done to determine the definitive cause of Cold AIHA, which showed bilateral multi-level cervical lymph nodes, bilateral enlarged axillary lymph nodes and multiple diffuse lytic areas involving the whole spine, as shown in Figures 1–3.

An ultrasound-guided true-cut biopsy was done over the left axillary lymph node and an immunohistochemical pattern was obtained which showed the presence of tumor cells arranged in cords and clusters. They have dark staining cells with mitotic activity (Figure 4). Microscopic staining including cytokeratin AE1/AE3 and cytokeratin 7 came out to
be positive suggestive of carcinoma of Breast origin. A sample for CA 125 was sent, which was elevated, confirming the diagnosis of cold AIHA as a rare association with breast carcinoma. Further, estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) receptor testing were done, all of which turned out to be positive. The patient was started on pulse therapy of corticosteroids and was referred to the oncology department, where she underwent chemotherapy and radiotherapy as a palliative treatment for her metastatic breast cancer, and AIHA was managed accordingly.

3. Discussion

The term Cold agglutinins were first described by Landsteiner in 1903 [1]. Their pathophysiological action against red blood cells and blood vessels leading to hemolytic anemia and Raynaud’s syndrome were described later by Clough and Iwai [2,3]. Almost 27 years after Clough and Iwai, Schubothe coined the term cold agglutinin in 1953 [4]. Cold AIHA is a rare condition caused by an increase in the level of cold-reactive antibodies. Mostly, it has been reported in patients with lymphoproliferative disorders including Non-Hodgkin lymphoma or Chronic lymphocytic leukemia (CLL) [5,6]. Autoimmune disorders including rheumatoid arthritis, systemic lupus erythematosus (SLE), scleroderma, ulcerative colitis, and Crohn’s disease are also a significant cause of AIHA [7,8]. Infectious diseases like viral infections, mycoplasma pneumonia, and various drugs like methyldopa, penicillin, cephalosporin, and NSAIDs can also cause AIHA [9]. The rarest association of AIHA is with solid malignancies [10]. In 2010 a meta-analysis was conducted over a period of 1945 to 2009 on AIHA patients having solid malignancies, 52 subjects were included in the study with a median age of 38–76 years, the most prevailing cancer reported by Joe et al. was renal cell carcinoma, Kaposi sarcoma (the time before the beginning of Anti-retroviral therapy), and non-small-cell lung carcinomas in decreasing pattern of hierarchy. AIHA has also been rarely associated with a variety of other cancers including testis, ovaries, prostate, and breast [11].
The presentation of AIHA is consistent with signs of anemia, jaundice, splenomegaly, reticulocytosis, raised serum bilirubin and a positive Direct Antiglobulin Test (DAT) [12]. After the positivity of the Direct antiglobulin test, monospecific DAT is done to differentiate between warm and cold antibodies. If the reaction is positive with only anti IgG but negative with anti C3d, the diagnosis of warm AIHA is made. If the reaction is positive with both anti IgG and anti C3d, it also indicates warm autoantibodies which is more frequently seen in patients with systemic lupus erythematosus (SLE) or idiopathic cause. If the testing came out to be positive for anti C3d but negative for anti-IgG, then it is labeled as Cold AIHA [13] as was seen in our patient.

In most of the cases, AIHA is idiopathic, but it is important to distinguish its idiopathic variant from other non-idiopathic variants, like bone marrow infiltration by the tumor as was seen in our patient, since the treatment and prognosis of the disease vary accordingly. The confirmation is made based on DAT testing. Another important cause of non-idiopathic variant was drugs. The most commonly involved drugs are antimicrobials including cefotetan, piperacillin or ceftriaxone. The easiest and only way to support a diagnosis of drug-induced hemolytic anemia is by taking informed consent and withdrawing the drug and see if the clinical picture of the patient improves or not [14].

Our case presents a 43-year-old elderly Asian woman who presented with subtle symptoms of fever, low energy, easy fatigability, shortness of breath, cough (aggravated on exposure to cold), lethargy with severe pallor and lymphadenopathy seen in two pectoral group of lymph nodes, hemoglobin of 4.49g/dL, serum total bilirubin of 2.63 umol/L, reticulocyte count of 1.05% and positive direct Coombs test, making the suspicion of AIHA secondary to non-Hodgkin’s Lymphoma, CLL or any other rare solid malignancy. The definitive diagnosis was made on Monospecific Coombs test for C3d which was positive, confirming the diagnosis of Cold AIHA. CT scan of neck, chest, abdomen, and pelvis was done to determine the primary source causing this AIHA, which showed bilateral multi-level cervical lymph nodes, bilateral enlarged axillary lymph nodes and multiple diffuse lytic areas involving the whole spine and pelvic girdle. An ultrasound-guided true-cut biopsy was done over left axillary lymph node, which showed tumors cells arranged in cords and clusters, the immunohistochemistry showed positivity for cytokeratin AE1/AE3 and cytokeratin 7, making a suspicion of breast cancer as a primary source, which was confirmed by elevated Cancer Antigen 15–3 (CA 15–3). Gene testing was sent for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) which came out to be positive confirming the diagnosis of Cold AIHA associated with triple-positive breast carcinoma.

Steroids are the mainstay of treatment for AIHA, but the definitive treatment depends upon treating the underlying cause. Steroids are effective in 70–80% of patients [15–17]. The remaining 20–30% are steroid-resistant which usually give response to other immunosuppressive agents like azathioprine, infliximab, cyclophosphamide or intravenous immunoglobulins. If response is not achieved with these immunosuppressants, splenectomy is considered as a last resort of treatment for AIHA [15].

4. Conclusion

Our report highlights a case of a 45-year-old female diagnosed with cold AIHA in association with metastatic breast carcinoma. The association of AIHA with solid tumors is rare, but its association with metastatic breast cancer is the rarest among all solid malignancies [10]. So, whenever we come across a patient with AIHA, in addition to treating it with steroids and other immunosuppressive therapeutic agents, the primary cause should be figured out and managed accordingly.

Disclosure statement

No potential conflict of interest was reported by the authors.

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