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Autoimmune Hemolytic Anemia as a Paraneoplastic Syndrome

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Abstract: ***Paraneoplastic autoimmune hemolytic anemia is a rare syndrome. It has been mostly recognized in association with lymphoproliferative disorders and to a much lesser extent in association with solid organ tumors. It has been reported in cases of breast, ovarian, prostate, thymic and renal cancer. The onset and severity is variable. Although it is rare, but should be considered in the differential diagnosis of anemia in patients with malignancy. Keeping high suspicion index is key to diagnosis. It resolves with tumor eradication or excision. Recurrence of hemolysis after a period of cancer remission could point towards relapse.***

Keywords: autoimmune hemolytic anemia, solid tumor, paraneoplastic syndrome

1. Introduction

Autoimmune paraneoplastic phenomena are generally rare. Paraneoplastic autoimmune hemolytic anemia (AIHA) is reported with different types of malignancies; however, it is a rare finding. It is mostly reported in association with hematologic neoplasms. In an analysis of solid tumor cases with paraneoplastic AIHA, majority were secondary to lung, colorectal, renal and Kaposi's sarcoma [1]. The exact pathogenesis of this hemolytic process in the context of cancer is not fully understood. Similar to other paraneoplastic processes, it could be possibly caused by neoplasm-secreted peptides or hormones or immune cross-reactivity between the neoplastic cells and host tissues [2]. As a result of its rarity, it is difficult to determine its prevalence; however, one study estimated a prevalence of up to 8% of paraneoplastic syndrome in cancer patients [2]. It is important to mention that the occurrence of paraneoplastic AIHA could be synchronous or asynchronous with the cancer diagnosis and treatment.

2. Literature Survey

Paraneoplastic autoimmune hemolytic anemia was initially reported in a benign dermoid cyst of the ovary in 1938, following that the association was described in a patient with pseudomucinous cystadenocarcinoma in 1945 [3],[4]. Paraneoplastic AIHA has been reported with several types of cancers affecting solid organs like breast, lung, colorectal, ovaries, prostate and kidneys. Benign tumors such as thymomas have been reported to be associated with AIHA. Published cases of paraneoplastic AIHA in association with solid organ tumors are quite limited. There are 10 cases of ovarian malignancies associated with AIHA reported in the literature six of which were associated with papillary cystadenocarcinoma [5]. Other reported cases were in patients with breast, prostate and renal cancer.

3. Discussion

Autoimmune hemolytic anemia is the destruction of red blood cells (RBCs) that results from the formation of autoantibodies directed against those cells. It is classified as warm or cold or mixed depending of the type of the antibodies formed. In the former, direct Coomb's test (DCT) is positive with anti-IgG. In the cold type, DCT is positive with anti-C3 and anti-IgM. In the later, DCT will be positive with anti-IgG, IgM and C3. Half cases of AIHA are idiopathic and the other half is caused by malignancies, infections or other autoimmune disorders. It has been estimated that approximately 11% of chronic lymphocytic leukemia patients develop AIHA. The incidence of AIHA is 1:100000 [6]. The peak incidence is in the seventh decade of life, which correlates with a rise in lymphoproliferative disorders associated with age [7]. AIHA presents with anemia which could mild, severe or even fatal. Paraneoplastic AIHA could pre-date the diagnosis of underlying malignancy or occurs after the diagnosis and treatment of the neoplasm. In AIHA, the destruction of RBCs takes place in the reticuloendothelial system (RES). This destruction results clinically in a picture of jaundice, anemia and splenomegaly. Laboratory tests will show raised indirect bilirubin and lactate dehydrogenase (LDH) with a low serum haptoglobin and positive DCT (see above). There is approximately 3% of warm AIHA cases that are DCT negative. Blood film will show spherocytosis. As it is extravascular hemolysis, urine haemoglobin and urine hemosiderine will be absent. Table 1 illustrates the laboratory features of AIHA. The exact pathogenesis of paraneoplastic AIHA is not fully understood. It is theoretically attributed to the possible formation of peptides and secretion of hormones by neoplastic cells or immunological cross-reactivity. Another study has attributed hemolysis to the release of a hemolytic serum factor from neoplastic cells after irradiation [8]. The trigger for hemolysis is not clear and this area needs to be discovered and studied further. It is important to say that the onset of paraneoplastic autoimmune hemolysis is variable and does not necessarily happen as an initial presentation. In fact it could present a feature of cancer progression or relapse after a period of remission.

Table 1: Laboratory features in AIHA

Elevated indirect bilirubin
Low hemoglobin
Elevated LDH
Low serum haptoglobin
Coomb's test positive
Raised retics count
Bilirubinuria
Absent hemosiderinuria
Absent hemoglobinuria

It is good practice nowadays to consider CT scanning of the neck, thorax, abdomen and pelvis as a part of the work up for AIHA. This will help identifying an occult malignancy that could be the potential cause of hemolysis. The mainstay of treatment of AIHA is treatment of the underlying cancer. Paraneoplastic AIHA would resolve when the neoplasm is excised or eradicated by radiotherapy or chemotherapy. Failure of resolution could possibly relate to another possible underlying disease process. Steroids also can be used in treating AIHA to suppress the production of autoantibodies. In aggressive life-threatening hemolysis, the priority is to stabilize the patient with urgent transfusion and commencing steroids with or without intravenous immune globulin (IVIG) and seeking expert advice. Transfusion is best to be avoided if not clinically indicated (asymptomatic and hemodynamically stable patients). In cases of refractory hemolysis, rituximab or splenectomy should be considered. It is important to mention that early recognition of this paraneoplastic syndrome could potentially lead to early cancer detection and treatment and possibly better outcomes.

4. Conclusion

Paraneoplastic AIHA is one of the paraneoplastic conditions that could be associated with solid organ tumours. It is more common with lymphoproliferative malignancies. Anemia in patients with cancer has got multiple causes and AIHA is one of these causes. Its onset is metachronous, hence its recurrence after cancer remission could possibly indicate relapse. Severity is variable but could be life-threatening. It is important to keep a high suspicion index to diagnose it. It potentially resolves after tumor eradication or excision. Early recognition could improve prognosis.

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