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Thrombocytopenia in Solid Tumors

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ABSTRACT

Thrombocytopenia in patients with solid malignancy can be caused by bone marrow involvement or toxicity from anticancer therapy; however, it could rarely be the first presentation of a tumor such as breast cancer or lymphoma. Hematological paraneoplastic syndromes such as paraneoplastic thrombocytopenia and/or immune thrombocytopenic purpura (ITP) are well described as secondary findings simultaneously with malignancies such as breast cancer and lymphoma. Other hematological conditions such as severe amegakaryocytic thrombocytopenia, thrombotic thrombocytopenic purpura (TTP), and myelodysplastic syndromes (MDS) have also rarely been described as a possible paraneoplastic process complicating solid tumors. On the one hand, occult disseminated malignancy may mimic ITP and TTP, leading to diagnostic and therapeutic problems. On the other hand, thrombocytopenia could be the first manifestation of cancer.

Keywords: paraneoplastic immune thrombocytopenia, thrombotic thrombocytopenia, solid tumors

INTRODUCTION

Thrombocytopenia is a common problem in oncology. It is often related to a treatment effect from cytotoxic agents or is the result of bone marrow involvement. Thrombocytopenia could rarely be the first presentation of a solid tumor such as breast cancer or lymphoma. It is debatable whether these represent incidental findings of two existing common pathologies or a paraneoplastic “distant” manifestation of cancer. This is a review of thrombocytopenia in solid tumors not caused by bone marrow involvement or by toxicity from anticancer therapy.

Paraneoplastic syndromes are systemic manifestations of cancer that cannot readily be explained by the local or metastatic effects of a tumor or of hormones indigenous to the tissue in which the tumor arises. The syndromes fall into four broad groups in which the patient has endocrine, neurological, hematological/vascular, or dermatological disease [1]. Paraneoplastic syndromes can also be defined as “disorders caused by cancer, but not a direct result of cancer invasion of the affected tissue or organ”.

The first unequivocal paraneoplastic syndrome was probably described in 1865 by Armand Trousseau [1–3] who described migratory thrombophlebitis which affected some patients not known to be otherwise ill. The venous occlusions were often migratory, affecting one site, clearing spontaneously and then affecting another site. Trousseau indicated that the disorder which now carries his name [4] occurred because “the blood of cachectic persons has a strong tendency to coagulate” [3]. This was proven later to be correct [5]. Trousseau died in 1867 of the disease he had described i.e., migratory thrombophlebitis and predicted that he had an occult gastric cancer, which he did on autopsy [1, 6].

There is a plethora of publications in the field of neurological paraneoplastic disorders (more than 8000 in PubMed) but not in hematological paraneoplastic syndromes such as paraneoplastic thrombocytopenia and immune thrombocytopenic purpura (ITP).

Although paraneoplastic syndromes are rare, their recognition by the physician is important for several reasons. In some patients, symptoms precede the diagnosis of cancer, and this can lead to the detection of an otherwise occult cancer that could potentially be curable.

In patients known to have cancer, paraneoplastic syndromes may be confused with metastatic or non-metastatic complications of cancer. Obviously, other potentially reversible causes must be carefully excluded before a diagnosis of a paraneoplastic syndrome is made. A number of paraneoplastic antigens are frequently expressed in the general population of cancer patients, and these may elicit tumor immune responses in the absence of autoimmune disease.

Thrombocytopenia and Malignancy

The primary regulator of the platelet count in humans is thrombopoietin, a glycoprotein that is produced primarily in the liver and cleared primarily by platelets and their precursors [7, 8]. Thrombopoietin induces the growth and development of megakaryocytes [9]; levels fluctuate with changes in platelet count due to variations in clearance. Interleukin-11 induces a modest increase in platelet counts, but is not required for thrombopoiesis [10–12]. Thrombocytopenia that is encountered in an oncology
practice may be caused by the effects of both cytotoxic chemotherapy and novel agents such as bortezomib or after multiple cycles of treatment with thrombocytopenic medication. Other causes include liver disease with decreased thrombopoietin levels, immune destruction, particularly in patients with lymphoid malignancies or infection with the human immunodeficiency virus, and sequestration.

**IMMUNE THROMBOCYTOPENIC PURPURA AND MALIGNANCY**

ITP is the one of the most common autoimmune disorders. It results from accelerated platelet destruction after the binding of autoreactive antibodies to platelets [13]. It is estimated that this entity affects approximately 1 in 10000 people among the general population. Most patients with ITP have detectable immunoglobulin (Ig)G and IgM antibodies against platelet glycoprotein complexes on their platelets or in their plasma [14].

**ITP AND BREAST CANCER**

In the published oncology literature, most patients with ITP concurrently with breast cancer had a prolonged interval between the two diseases, suggesting that ITP and breast cancer were completely coincidental [15–21]. Unless splenic metastasis or bone marrow infiltration by tumor cells is shown by radiological, scintigraphic, or histopathologic examinations, the association between ITP and breast cancer could probably be considered unrelated, i.e., not paraneoplastic. ITP may respond to steroid therapy before the diagnosis of breast cancer and during the follow-up period. In the small number of reported cases of ITP and breast cancer, curative surgery followed by adjuvant chemotherapy in early breast cancer did not prevent the relapse of ITP in the postoperative period. Stable platelet counts have been maintained in patients who had chemotherapy, although the reported follow-up has been relatively short.

Of the 21 reported cases, only two patients had splenic metastasis from breast cancer [23], and bone marrow metastasis was present in seven of the 21 cases (30%) [16–21]. Immune-mediated platelet destruction and the presence of serum platelet agglutinins in solid tumors associated with ITP are possible reasons in the patient without any evidence of metastases [17].

Often in patients with ITP and a new presentation of breast cancer, there is a concern about the safety of adjuvant chemotherapy in the face of thrombocytopenia. Immunosuppression from corticosteroids and/or chemotherapy often increases the platelet count, albeit temporarily. Therefore, the presence of a diagnosis of ITP should not prohibit breast cancer patients from receiving adjuvant chemotherapy. With the advent of therapies involving novel non-cytotoxic mechanisms of action, new challenges will be encountered. For instance, there are no reports on the effect of antiangiogenic agents such as bevacizumab on ITP. With the introduction of these agents into clinical practice, this question will need to be addressed in future clinical trials.

**ITP AND HODGKIN LYMPHOMA (HL)**

The simultaneous occurrence of autoimmune disorders such as ITP and Hodgkin lymphoma (HL) is not very uncommon [23–25]. A review of the British National Lymphoma Investigation (BNLI) registry reported eight patients with ITP in association with HL. The patients were heterogeneous for initial stage of HL, histology, and treatment received. The median time from diagnosis of HL to diagnosis of ITP was 23 months (range 3–57 months). Six of eight patients were in complete remission at diagnosis of ITP, one was in relapse, and one was undergoing first-line chemotherapy. Of those patients developing ITP in remission, only one subsequently relapsed. The ITP responded to a single course of oral prednisolone in six of the eight patients. Thus, the occurrence of ITP in patients with HL was interpreted to be independent of the activity of the lymphoma, responding to therapy as for primary ITP without a prognostic significance [26].

**ITP AND NON-HODGKIN LYMPHOMAS (NHL)**

ITP is a relatively common immuno-hematologic complication in non-Hodgkin lymphomas (NHLs) and may complicate the treatment. A retrospective analysis from a single Austrian center combined with previously published cases of NHLs (excluding chronic lymphocytic leukemia) associated with ITP was published [27]. The prevalence of ITP in NHL (without chronic lymphocytic leukemia) in four large studies (1850 patients) was 0.76% (range 0–1.8%). The highest prevalence of ITP was in the following lymphoma subtypes: follicular lymphomas 1.2%, marginal zone lymphoma 4%, mantle cell lymphoma 9%, and T-cell lymphomas 11.1% [27]. Similar to the reported cases with simultaneous breast cancer and ITP, about half the patients had ITP prior to the diagnosis of lymphoma. No sustained remissions were documented in patients treated with steroids alone. On the other hand, sustained complete remissions were observed after specific antilymphoma therapy. Chemotherapy was the best treatment in many NHL patients with ITP compared with standard treatment for ITP. However, ITP in patients with NHL was a complicating factor adding new challenges to the treatment of these patients [27].

**ITP AND OTHER SOLID TUMORS**

There are two individual reports of patients with lung cancer presenting with ITP. Both cases were from Japan, and the ITP is reported to have stabilized after treatment of the lung cancer in both cases. In one patient, treatment was surgical, and the other patient received chemotherapy containing cisplatin and etoposide [28, 29].

Individual case reports with ovarian, esophageal, gastric, and pancreatic adenocarcinoma presenting as ITP have also been reported [30–33].

**SOLID TUMORS AND THROMBOCYTOPENIA FROM MYELODYSPLASTIC SYNDROME (MDS)**

Severe amegakaryocytic thrombocytopenia and MDS have rarely been described as a possible paraneoplastic process complicating solid tumors, including lung cancer [34].
Although varying degrees of thrombocytopenia are seen in approximately 25% of patients with MDS, it is unusual for the disease to present with isolated, severe thrombocytopenia [35].

In addition, amegakaryocytic thrombocytopenia has been described as a paraneoplastic syndrome complicating thymoma and NHL [36, 37]. In a cohort of 155 patients with MDS, 21 presented with malignant solid tumors. Myelodysplasia was present after the diagnosis of cancer in eight patients (interval between the diagnosis of both conditions, 18 months; median survival, 49.5 months), simultaneously with diagnosis in 11 (median survival, 8 months), and before malignancy in two patients (interval between the diagnosis of both conditions, 47 and 7 months). In this cohort, one patient was given chemotherapy for lung cancer, and three patients received radiotherapy for adenocarcinoma of the kidney and cancer of the prostate. At the time of diagnosis of MDS, nine patients already presented metastatic spread. Fourteen patients died, 10 as a result of tumor-related complications, and four because of transformation to acute leukemia [34].

MDS patients present a higher incidence of malignant tumors than the general population [35]. The occurrence of MDS in cancer patients may be considered to be related to the tumors than the general population [35]. The occurrence of MDS in cancer patients may be considered to be related to the malignancy rather than an independent phenomenon [35].

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) AND MALIGNANCY

Thrombotic thrombocytopenic purpura and the hemolytic uremic syndrome (TTP-HUS) are related and uncommon disorders with a high fatality and complication rate if untreated. Plasma exchange therapy has been shown to produce high response rates and improve survival in patients with many forms of TTP-HUS. Patients with disseminated malignancy who present with microangiopathic hemolytic anemia and thrombocytopenia may be misdiagnosed as TTP, resulting in inappropriate plasma exchange treatment, a procedure with major risks, and delay of appropriate chemotherapy.

A retrospective cohort study of 178 consecutively treated patients with TTP-HUS analyzed whether clinical or laboratory characteristics could predict for important short- and long-term outcome measures. One hundred and seventy-one patients (96%) received plasma exchange as the principal treatment. The rate of complete response was 65% or 55%; the rate of relapse was 18%. Seventy-two percent of the cohort had an idiopathic TTP-sporadic HUS, whereas 17% had an underlying cancer. The estimated overall 5-year survival was significantly worse in those with an underlying cancer [38].

A registry review of TTP-HUS has reported that 10 of 351 patients who were initially diagnosed with TTP and treated with plasma exchange were subsequently discovered to have disseminated malignancy [39]. Only one patient had a history of cancer. In these 10 patients, neurologic abnormalities, hematocrit, platelet count, and serum creatinine were not different from the 133 concurrent patients with idiopathic TTP.

The final diagnoses included eight different malignancies: breast carcinoma (two patients), non-small cell lung cancer (two patients), pancreatic carcinoma, renal carcinoma, myelodysplasia (refractory anemia with excess blasts), acute lymphoblastic leukemia, diffuse large B-cell lymphoma, and Kaposi’s sarcoma (one patient each).

Patients with disseminated malignancy had a longer duration of symptoms, more frequent presence of respiratory symptoms, higher lactate dehydrogenase levels, and more often failed to respond to plasma exchange treatment. Diagnosis of malignancy was made by bone marrow biopsy in six patients but not until autopsy in two patients [39].

A systematic literature review identified 19 additional patients, reported from 1965 to 2005, in whom TTP or HUS was initially suspected and systemic malignancy was subsequently discovered. Fourteen different malignant disorders were diagnosed in these 29 patients [39].

In another retrospective series, out of 77 patients with the primary diagnosis of TTP, nine had active cancer. Six patients had the classical triad of TTP, but three patients had thrombocytopenia and microangiopathic hemolytic anemia. Among the seven patients who had TTP in the absence of chemotherapy during the three preceding months, six had bone marrow metastasis with secondary myelofibrosis. None of those patients was known to have idiopathic myelofibrosis prior to the diagnosis of TTP, and splenomegaly was not present [40].

Occult disseminated malignancy may mimic TTP. A search for systemic malignancy, including a bone marrow biopsy, is appropriate when patients with TTP have atypical clinical features or fail to respond to plasma exchange.

CONCLUSIONS

Thrombocytopenia could rarely be the first presentation of a solid tumor such as breast cancer or lymphoma. Hematological paraneoplastic syndromes, such as paraneoplastic thrombocytopenia and ITP, are rare but well described in several malignancies including breast cancer and lymphoma. Other hematological conditions such TTP and MDS have also rarely been described as possible paraneoplastic processes complicating solid tumors. Furthermore, occult disseminated malignancy may mimic TTP. When thrombocytopenia occurs during the course of a solid tumor, with no obvious clinical and laboratory relationship, it can be speculated that this could be an immunologic mechanism and is rarely the first manifestation of the neoplasm. A search for systemic malignancy in these circumstances is warranted.

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REFERENCES


