Case Report:

Squamous cell carcinoma larynx presenting as idiopathic thrombocytopenic purpura

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ABSTRACT

Association of immune thrombocytpenic purpura with solid malignancy as paraneoplastic manifestation has been reported earlier mainly with lymphoma and breast cancer**.** We report the case of a patient with squamous cell carcinoma of the larynx presenting with idiopathic thombocytopenic purpura (ITP). A 67-year-old lady presented with multiple ecchymotic patches and petechiae all over the body and bleeding from oral cavity was found to have severe thrombocytopenia diagnosed as ITP with bone marrow evidence of peripheral destruction without infiltration of bone marrow. Five months later she was diagnosed to have squamous cell carcinoma of larynx. Platelet count improved after splenectomy.

Key words: *Immune thrombocytopenic purpura, Splenectomy, Squamous cell carcinoma larynx, Paraneoplastic syndromes*

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INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP) is characterized by thrombocytopenia, presence of antibodies to platelet membrane antigens, hypercellular or normal bone marrow with evidence of peripheral destruction of platelets**.** ITP is associated with many conditions like infections, neoplasms, thyroid disease. It can be the initial manifestation of systemic lupus erythematosis or lymphoproliferative disorders. The increased platelet destruction may be due to antibody binding,immune complex deposition,or antibody mediated complement activation.[1] Thrombocytopenia is commonly seen in oncologic practice, resulting from chemotherapy induced bone marrow suppression or due to bone marrow infiltration by tumours. ITP can be the initial manifestation of an underlying malignancy whether it is merely a coincidental association or a paraneoplastic manifestation of the tumour is still debatable. Association of chronic lymphatic leukemia with ITP has been described.[2] The onset of ITP bears no relationship to the severity or the duration of chronic lymphatic leukaemia (CLL) and does not have any prognostic significance.

There are several published articles regarding the association of ITP with breast cancer and Hodgkin's lymphoma.[3,4] Hodgkin's lymphoma developing simultaneously with ITP has also been described. In a retrospective analysis of ITP in patients with non-Hodgkin's lymphoma[5] the highest prevalence of ITP was noted in mantle cell lymphoma (9%) and T-cell lymphoma (11.2%).[5] A syndrome resembling ITP in 10 patients with diverse forms of cancer has been described.[6] In this study, ITP was associated with various cancers like CLL, large cell and oat cell carcinoma of the lung, adenocarcinoma rectum and gall bladder, acute lymphoblastic leukaemia, Hodgkin's lymphoma, among others etc.

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Squamous cell carcinoma larynx presenting as ITP is a rare association. Only one case report of carcinoma of vocal cord associated with ITP has been reported.[7] ITP could be the paraneoplastic manifestation of malignancy, stressing the need for active search for malignancy when ITP precedes the manifestation of malignancy.

CASE REPORT

A 67-year-old lady with no pre-morbid illnesses presented with bleeding from the mucosa of cheek, brownish discolouration of the tongue and at multiple sites on the body including chest and extremities of four days duration. There was no history of haematemesis, malena, hematuria. She was a chronic tobacco chewer. On examination she had multiple petechiae and ecchymotic patches on the body with hyperpigmentation at dorsum and ventral aspect of tongue.There was an active bleed from the mucosa of cheek. There was no splenomegaly nor any significant lymphadenopathy noted. Ultrasound abdomen did not reveal any splenic enlargement or intra abdominal lymph nodes.

Laboratory investigations revealed a platelet count of 2000/mm^3 (normal 150,000-400,000 s/mm^3), total leucocyte count 17,000/mm^3 (normal 4000-11000/mm^3), haemoglobin 11.2 g/dL (normal 13-15 g/dL). Liver function tests were normal. Prothrombin time and activated partial thromboplastin time were normal. Peripheral smear showed markedly decreased platelets with no evidence of fragmented red blood cells and bone marrow aspiration showed cellular marrow with increased megakaryocytic activity suggestive of peripheral destruction of platelets (Figures 1A and 1B). Bone marrow biopsy did not reveal any infiltration. Antiplatelet antibody was negative.

She was diagnosed to have ITP and started on intravenous methyl prednisolone 1 g/day for 3 days followed by oral prednisolone 60 mg/day with transfusion of several units of platelets rich plasma. Her platelet count was widely fluctuating between 3,000 mm^3 to 35,000/mm^3, requiring intermittent platelet transfusions. We started her on intravenous Vincristine 1mg bolus once a week, planning to give for 4 weeks, but with 2 doses one week apart her platelet count increased to 160,000 and then stabilized at 360,000/mm^3 with corticosteroids treatment for almost 2 months. But when we tried to taper down corticosteroid treatment her platelet count fell down to below 10,000 and she had fresh ecchymotic lesions requiring

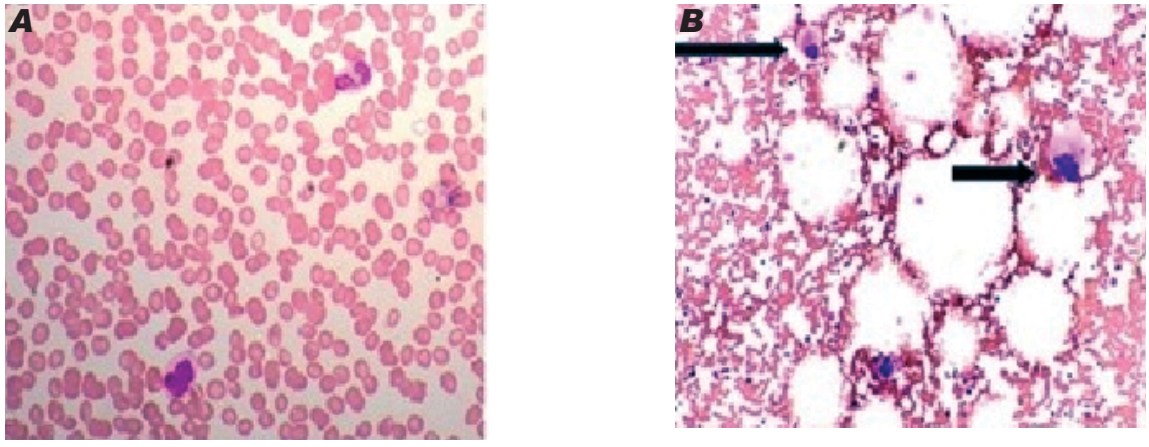
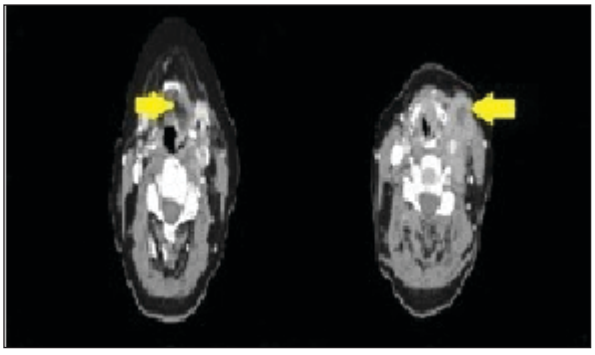


Figure 1: Photomicrograph of peripheral smear showing markedly reduced platelet count (Leishman, · 400) **(A)**. Photomicrograph of bone marrow aspiration showing increased megakaryocytes **(B)** (arrows) (Leishman, · 100)

platelet transfusion.She was planned for splenectomy. With single donor platelet transfusion she had undergone splenectomy and the postoperative period was uneventful and platelet count remained above 200,000/mm^3 thereafter. Steroids dose was slowly tapered-off and stopped.

Two months later she came to out-patient department with history of swelling on the left side of the neck with weight loss and hard lymph node was palpable. Ultrasonography of the neck was suggestive of a neoplastic mass at left side of the neck in muscular planes with infiltration to adjacent structures with multiple metastatic nodes. Fine needle aspiration cytology was done which revealed squamous cell carcinoma. Indirect laryngoscopy showed slough covered ulcerative lesion on the arytenoid and the aryepiglottic fold with decreased movement of left vocal cord. CT scan confirmed the findings (Figures 2A and 2B).Direct laryngoscopy and biopsy from the lesion revealed moderately differentiated squamous cell carcinoma of the larynx (Figure 3) on histopathological examination. She was advised to undergo total laryngectomy with bilateral neck dissection but was not willing for the same. Hence palliative chemotherapy was advised. Platelet count remained above 200,000/mm^3 through out this period. Two weeks later she came to emergency department with breathing difficulty and emergency tracheostomy was done. Subsequently, the patient was lost to follow-up.



Figures 2; CECT showing a growth involving the left side of the supraglottis (A); necrotic lymph node mass in the left side of the neck (arrow) (B)

DISCUSSION

Chronic ITP is common in adults. The disease affects women more often than men; 70% of those women were less than 40 years of age. In ITP like syndrome described with 10 diverse forms of cancer, more than 70% of patients were more than 40 years old and more than 50% of them were above 60 years of age.[6] When ITP develops in elderly person above 60 years of age, it could be the hematologic paraneoplastic manifestation of a cancer, hence an active search for the underlying malignancy is necessary. ITP can develop before, simultaneously or after the diagnosis of cancer. Several publications in oncology literature revealed occurrence of ITP with breast cancer.[4] Most of these patients had prolonged interval between the two diseases hence ITP could be a coincidental finding. Out of 21 reported cases 2 had splenic metastasis and seven (30%) had bone marrow infiltration by tumour. Curative surgery followed by chemotherapy for breast cancer did not prevent the relapse of ITP. Autoimmune disorders such as ITP can occur simultaneously with Hodgkin's lymphoma . The British National Lymphoma Registry reported 8 patients with ITP with Hodgkin's lymphoma. Median time from diagnosis of lymphoma and ITP was 23 months (range 3-57 months). Six patients were in complete

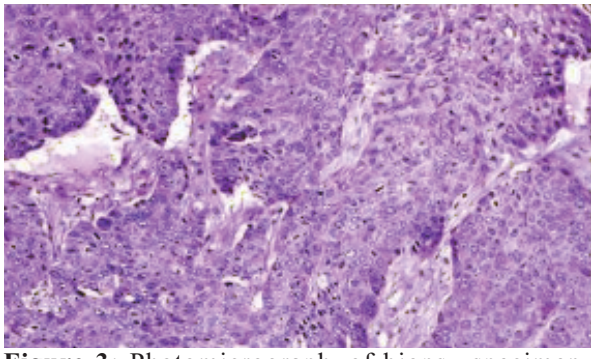


Figure 3: Photomicrograph of biopsy specimen obtained from the laryngeal growth showing a moderately differentiated squamous cell carcinoma (Haematoxylin and eosin · 200)

remission and, ITP responded to steroids. They interpreted ITP to be independent of the activity of the lymphoma. A retrospective analysis of non Hodgkins lymphoma showed increased prevalence of ITP in some lymphoma subtypes, half of them occurred before the diagnosis of lymphoma. Sustained improvement of ITP occurred only after the chemotherapy of lymphoma indicating a cause and effect relationship between ITP and cancer. [5] A syndrome resembling ITP with 10 diverse forms of cancer was published in which some cases ITP preceded the cancer, others occurred simultaneously and few manifested after the diagnosis of cancer.[6]

The definitive cause and effect relationship between solid tumours and ITP was demonstrated by two studies.[8,9] In one study[8] increased levels of platelet associated IgG and IgM antibodies were observed in three patients with carcinoma before and after treatment. Platelet associated antibody normalized in one patient with corticosteroid treatment and other responded partially to corticosteroids and required splenectomy and immunosuppressive therapy.[8] The level of platelet associated immunoglobulin G (IgG) and immunoglobulin M (IgM) antibody correlated with tumour mass at diagnosis and was more in third patient with progressive disease. Similarly the immunological nature of the platelet destruction was demonstrated in vitro by measuring platelet associated IgG antibody and decreased platelet survival was demonstrated using Cr^{51} labelled platelets and I^{131} fibrinogen kinetic assays among eight patients with solid tumours.[9]

The mechanisms of thrombocytopenia in malignancy are either by bone marrow infiltration, hypersplenism (as in lymphoma), autoantibodies (as in ITP) or disseminated intravascular coagulation. There is limited data on co existence of ITP and malignancy. The exact pathogenesis will be known when more data is available in the literature. The thrombocytopenia in patients with various solid tumours was thought to be due to immune mediated platelet destruction. It is proposed that aberrant humoral immune responses are responsible for the autoimmune diseases in malignancy, especially in CLL. Immune mediated platelet destruction and the presence of serum platelet agglutinins in solid tumours could be the possible reasons for the development of ITP in other solid tumours. It has been postulated that the antigens characteristic of tumour cells cross react with platelets or unknown immunologic factor released by cancer cells which may affect platelets, resulting in their destruction or increased consumption causing thrombocytopenia.[3] Tumours disseminate through blood stream and it is difficult to demonstrate single cancer cell from blood stream since there is no specific staining technique. Tumour cells have specific antigenic surface markers which can be detected by immunofluorescent antibody technique by which exact pathogenesis of ITP with tumour can be understood.[10] There is a need for specific immune test which can demonstrate certain factors released by tumours responsible for platelet destruction or antibodies against tumour cell antigens.

In our patient ITP preceded the diagnosis of cancer. The presentation of ITP was of very short duration (4 days) and thrombocytopenia was severe (platelet count < $2000/mm^3$). There was no hypersplenism nor splenic or bone marrow infiltration , and other cell lines were normal. Though the antiplatelet antibody was negative there was peripheral smear and bone marrow evidence of peripheral destruction of platelets. There was no clue regarding squamous cell carcinoma larynx since the patient did not complain of any hoarseness of voice or cough. The presentation of malignancy was acute with evidence of metastatic involvement of peripheral lymph nodes. ITP did not respond to corticosteroids but promptly

responded to splenectomy. All these indicate that ITP in this patient was the initial presentation of the tumour and response to splenectomy indicates the presence of autoantibodies to platelets probably from tumour antigens. Squamous cell carcinoma of lung presenting as ITP has been reported. Only one case report of carcinoma of vocal cord associated with ITP has been documented.[7]

ITP can be the initial manifestation of an underlying cancer. An active search for the cancer is required in all cases of ITP which is refractory to steroids especially in elderly population for the early diagnosis and management of an underlying malignancy.

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