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# Primary immune thrombocytopenia (ITP) and breast cancer. Case report and review of literature

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## Abstract

We present here a case report of a 71 year old female diagnosed with bilateral breast cancer and primary immune thrombocytopenia. Breast cancers were diagnosed on the basis of histopathology report and ITP was diagnosed after excluding all the diseases that can cause thrombocytopenia like SLE, antiphospholipid syndrome etc. and as the platelet level was under 100 G/l. (International working group definition). Initially the patient was treated with hormonal therapies(aromatase inhibitors, exemastane, LHRH analogues , magestrol ), after which the patient was treated with 6 cycles of palliative chemotherapy with protocol AC( Doxorubicin, Cyclophosphamide) and 4 cycles of docetaxel as the disease got hormone refractory initially . For ITP, she was initially treated with encorton after which later consecutive treatments for ITP were intravenous immunoglobulins, cyclophosphamide, vincristine iv, rituximab iv and with danazol p.o.. ITP treatments were changed due to ineffectiveness of previous therapies. During the whole treatment, platelets counts increased from a lowest level of 7 G/l to the even 221 G/l (highest count); thus we could administer her, the above said chemotherapies.

**Keywords:** ITP-Immune thrombocytopenic purpura (Primary immune thrombocytopenia); TPO-mimetic -thrombopoetin mimetics; ER-estrogen receptors; PR- progestron receptors; LHRH-Luteinizing hormone releasing; b.i.d-twice daily; G-giga ;SLE- Systemic Lupus Erythematosus

## Introduction

Breast cancer is a common disease and so is ITP, but coexistence of both diseases is rare. As per definition given by International Working Group, primary immune thrombocytopenia is platelet counts below 100 G/l, with no other cause of thrombocytopenia and no clinically evident secondary form of immune thrombocytopenia. 80% ITP is primary and 20% ITP is secondary ie due to certain states like for example connective tissue systemic diseases, anti-phospholipid syndrome, lymphomas , infections , drugs etc.ITP can also be divided as newly diagnosed (less than 3 months), persistent (3-12 months) and chronic ITP (if it exists more than 12 months).

Primary immune thrombocytopenia (ITP) is a disease involving antibody and cell mediated destruction of platelets and suppression of platelet production. It it now known that it is the autoantibody production against certain glycoproteins (gp IIb/IIIa) which is the underlying cause of the disease, but what triggers the production of this autoantibody is unknown. Probably it is likely that more than one etiology is involved. Demographics of ITP has changed from high prevalence in children, adolescents and young adults with female predominance in 1960s to predominantly older individuals with no gender difference.

## Case report

71 year old female diagnosed with bilateral metastatic cancer patient presented to our department in December 2014 with thrombocytopenia (PLT-7 G/L)-lowest count. This patient was directed to us by an oncology institute for further hematology/ oncology treatment. This patient had been a known case of thrombocytopenia from 2004. Thrombocytopenia initially was mild (Platelet count: 60-70 G/l).This mild thrombocytopenia was stable until 2014. After which further decrease in platelet count was observed. After which the patient had a bone marrow biopsy done, where it was found that she has local foci of infiltration of ca breast, normal megakaryopoiesis. After exclusion of all the other reasons of thrombocytopenia for example diseases like SLE, antiphospholipid syndrome ,Evans syndrome and other causes , since the platelet count was under 100 G/l , a diagnosis of ITP was established. After which the patient was treated as for ITP. The platelet count increased from 7 G/l (December 2014) to 221 G/l (2015). After attaining a satisfactory platelet level of 75 G/l and above, she was treated for metastatic breast cancer. We administered 6 cycles of AC (Doxorubicin, Cyclophosphamide) protocol attaining PFS of 1 months. When the disease progressed we administered 4 cycles of Docetaxel mono therapy attaining PFS of 9 months. A detailed chronology of events is shown below to elaborate the problems faced and how we resolved them.

## Analysis of Trephine biopsies (Bone marrow biopsies)

Before establishing a final diagnosis of ITP the patient had undergone trephine biopsies thrice. 2 Two trephine biopsies were done just before establishing the diagnosis of ITP. The myelogram clearly mentioned

1.Bone marrow was not aplastic rather in one of the biopsy reports it was mentioned that bone marrow was hypercellular.

2.However it was found in one of the myelograms that there is infiltration of bone marrow with breast cancer cells but then megakaryopoeisis was intact and platelet producing megakaryocytes were present in the bone marrow. Tumour infiltration to the bone marrow was minimal and was not considered to be a reason of severe thrombocytopenia in this case. Moreover breast cancer infiltration rarely cause bone marrow suppression to the extent that platelet levels fall to 5G/l or 7G/l as it happened to our patient.

All other hematological diseases /disorders, blood cancers were excluded in the bone marrow biopsies done that could be the reason of thrombocytopenia.

## Exclusion of other factors which may cause thrombocytopenia

Other reasons for thrombocytopenia like viral diseases (HIV, Varicella zoster etc.) were ruled out. She did not have a history of DIC or TTP. Heparin induced autoimmune thrombocytopenia was excluded as she was not on heparin injections. She did not have any history of autoimmune disorders like SLE, antiphospholipid syndromes, autoimmune lympho proliferative syndrome (ALPS), common variable immune deficiency (CVID) etc.

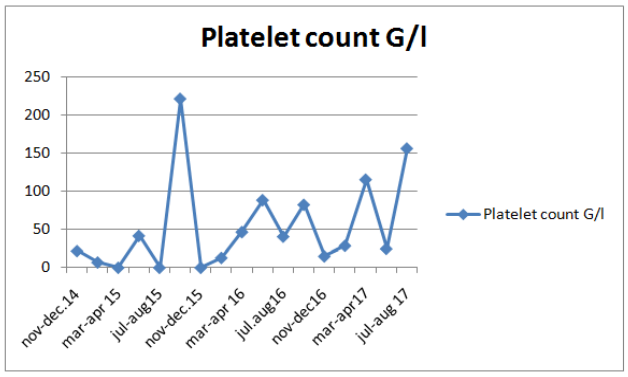


**Figure 1:**Diagram showing platelet counts at various time intervals. Details about platelet transfusions and treatments mentioned below (In chronology of events).

## Chronology of events

8.2.1995: FNAC of lump of left breast –cellulae carcinomatosae.

8.03.1995: Operation –radical mastectomy of left breast .Histopathology: carcinoma ductale invasivum mammae pT2N0(0/15)M0 ; ER,PR status: not known(not mentioned in histopathology report).

1.2.2000: During follow up mammography –microcalcifications in upper external quadrant of right breast.

28.03.2000: local incision of the right breast tumor .Histopathology: carcinoma ductale invasivum mammae G3 pT1bNxMx; ER, PR –status not known (not mentioned in histopathology report)

17.04.2000: Radical mastectomy of right breast

March 2004: thrombocytopenia was first observed, platelet counts approximately: 78 G/l; 80-91 G/l; 103 G/l.

July 2006: First bone marrow biopsy done (trephine biopsy)-where megakaryocytes were present which were producing platelets. From this point patient was under the observation of a hematologist.

May 2010: Pelvic bone metastasis detected, patient qualified and given palliative radiotherapy (20 Gray in 5 fractions).

November 2010: Bonefos (sodium clodronate)-oral biphosphonates started.

March 2011: Sternum(bone) metastasis detected, metastasis in pleura of both sides detected.

May 2011: Palliative hormonotherapy – aromatase inhibitors (Arimidex) started, after which stabilization (metastatic lesions in pleura –stable on imaging). Since the patient's hormone status was not known, the pathology department was requested to establish hormone status, but the results were not conclusive .Thus country consultant - clinical oncology was asked for his opinion about the treatment. And after getting opinion of country consultant clinical oncology of Poland, patient was qualified for hormonal therapies as was the only option since the platelet counts were low.

August 2014: due to pain in pelvic bones, patient again qualified for palliative radiotherapy(20 gray in 5 fractions). Change of bifosfonates from oral biphosphonates (Bonefos) to pamidronate i.v..

June 2012: Fluid in pericardium detected.

February 2014: Progression of metastatic disease (increase in size of pleural metastasis), thus homonotherapy with aromatase inhibitors stopped and II line hormonotherapy with exemestane was started.

June 2014: Due to further progression of disease, III line hormonotherapy started with LHRH analogues.

September 2014: pericardiocentesis done due to increase of fluid in pericardium. Magesterol (progestins) with encorton started in small doses. Histopathology/ cytology of pericardial fluid: ER(+)100%; PR(+)100% ; TTF(-) metastasis of breast carcinoma.

November 2014: Platelet count-22 G/l; 10 G/l; 5 G/l. Patient was sent for hematology consultation . Disqualified for all oncological treatments by oncologists at previous oncology centre.

27 February 2015: Bone marrow biopsy (trephine biopsy) – Bone marrow film with high cellularity, Megakaryocytes seen, no

infiltration by cancer cells.

2 April 2015: bone marrow biopsy (trephine biopsy)- Infiltration of bone marrow by tumour cells. Immunohistochemistry staining: CKAE1+E3+.

7 May 2015: Diagnosis of ITP established, patient for the first time treated with intravenous immunoglobulin 1 g/kg of body weight –day 1 and day 2. Platelet count-42 G/l.

June 2015 to October 2015 : 6 cycles of palliative chemotherapy administered –protocol AC(Doxorubicin , Cyclophosphamide) .Increase in platelet count from 7 G/l (December 2014) to 221 G/l (19-October 2015) .

October 2015 to February 2016: ITP treatment with intravenous immunoglobulin (approximately every 3-4 weeks), platelet levels by and large at satisfactory levels.

February 2016: ITP treatment with combination of i.v. immunoglobulins. Platelet count increased from 13G/l to 41-47G/l.

June 2016: Due to progression of oncological disease (metastatic breast cancer) and satisfactory platelet count ( 89 G/l) patient was further qualified for II line palliative chemotherapy , protocol- docetaxel monotherapy ( 75% of prescribed protocol dose).

July 2016: ITP treated with iv immunoglobulin (dose 1 g/kg day 1 and day) Platelet count 41 G/l.

Received II cycle of docetaxel (75% of dose). Platelet count 68 G/l.

August 2016: Received III cycle of Docetaxel (75% of dose). Platelet count 101 G/l.

24 September 2016: Control CT Scan showed stabilization of metastatic breast cancer lesions.

September 2016: Received IV cycle of Docetaxel (75% of dose). Platelet count 83G/l.

September 2016: platelet count 39 G/l immunoglobulin in dose of 1 g/kg on day1 and 2.

30 september 2016: After 4 cycles of chemotherapy with docetaxel, decision was taken to stop chemotherapy.

November 2016: Control CT Scan showed stabilization of oncological disease .ITP treated with immunoglobulin 1 g/kg day 1 and day 2 i.v. and platelet count raised from 15 to 31 G/l. Trephine biopsy done.

January 2017: Treatment with zolendronic acid (4 mg.iv) started.

27 January 2017: Due to weak response of i.v. immunoglobulins, dose 1 g/kg day 1 and day ;(platelets 24 G/l), encorton was added to immunoglobulins for the treatment of ITP. As the platelet count was inadequate and patient needed oncological treatment, next line hormone therapy started with tamoxifen. Platelet count observed 24 G/l.

10 February 2017: CT scan done, regression of metastatic lesions in left lung pleura , but as per RESIST 1.1 criteria – stabilization of disease. Thus hormone therapy with tamoxifen continued.

14 March 2017: As the patient had type II DM, she had high blood glucose levels after encorton .So the family doctor decreased the encorton dose from 60mg to 40 mg. From march 14th again encorton given as per the recommended dose 60mg.Platelet count- 29 G/l.

14 April 2017: Steroids changed from encorton to solumedrol given along with intravenous immunoglobulins. No significant increase in platelet count (PLT-14 G/l). Patient qualified for vincristine intravenous therapy (1 mg iv ) to be given every week. On 14.03.17 received I cycle of vincristine.

21 April 2017: II cycle (dose 1 mg iv) of Vincristine, increase in platelet count observed from 11 G/l to 29 G/l.

28 April 2017: Platelet counts further increase to 116 G/l. Signs of hepatotoxicity observed; serum bilirubin level increased to 2,2mg/dl.. Thus next dose of Vincristine was not given.

12 May 2017: III cycle of Vincristine (1 mg) .Platelet count – 25 G/l.

23 May 2017: Increase in hepatotoxicity due to Vincristine .Vincristine stopped . For further treatment of ITP patient was qualified for next line treatment with Rituximab-dose 100 mg iv. – to be given every week. First cycle of Rituximab administered. A control CT scan done to access metastatic lesions of breast cancer: PR as per RESIST1.1.

30May 2017: II cycle of Rituximab (dose 100 mg iv), PLT-56 G/l.

7. June 2017: III cycle of Rituximab (dose 100 mg iv) .PLT -11 G/l, platelets transfused as patient had subcutaneous bleeding (bruises seen on arms).

22June 2017: Platelet count 9 G/l, bruises on arms of both upper extremities. Signs of subcutaneous bleeding observed, thus platelets transfused. Rituximab stopped. Patient qualified for next line treatment with danazol. Danazol started on a single dose of 200 mg once daily orally.

29June 2017: PLT-44 G/l, ITP therapy with danazol continued. Since single dose of danazol was well tolerated, dose of danazol was increased to b.i.d 200 mg daily (twice daily).

29June 2017: PLT-44 G/l, danazol (dose 200 mg b.i.d) continued.

22 August 2017 –PLT- 157 G/l , increase in serum transaminase levels observed. Dose of danazol decreased to 200 mg once daily.

September 2017: Presently patient in good condition (Karnofsky 90%), being treated with once daily 200 mg

danazol –continuing therapy of ITP. Metastatic breast cancer – disease stable with tamoxifen.

Thus in short with effective treatment of ITP (encorton, solumedrol, intravenous immunoglobulins, vincristine, rituximab, danazol), it was possible to administer chemotherapy protocols like AC (doxorubicin, Cyclophosphamide) and Docetaxel monotherapy. We chose Vincristine , cylophosphamide for treating ITP which no doubt acted as antineoplastic agents

too. As the patient was ER, PR positive she was treated with various hormonotherapies : Aromatase inhibitors, exemestane, LHRH analogues, magesterol and lastly with tamoxifen which gave us very promising results .There existed need of transfusing platelets when we saw signs of subcutaneous bleeding/ bruises/ petechiae and the platelet level was very low. During last control visit (September) platelet count before few days of publishing this case report was 157 G/l.

## Literature review

Individual case reports or case report of series of patients have been published, presenting patients with coexistent ITP with breast cancer (1) in a single centre series of 10 patients with breast cancer associated with primary immune thrombocytopenia suggested that there may be some correlation between these two diseases; they suggested that it may be tumor induced thrombocytopenia. Many authors hypothesize that it is some autoimmune mechanism which produce autoimmune antibodies. More and more ITP now are being categorized as secondary ITP as the underlying cause is known. After treating for example H.Pylori infection many secondary ITP gets cured if treatment of H. Pylori is started soon after infection (2) presented two cases of breast carcinoma diffusely metastatic to spleen incidentally detected after splenectomy done for ITP. An Interesting publication where these authors found breast cancer metastasis postmortem. Lack of discrete tumor mass in the spleen in such cases makes it very difficult to detect such metastatic cancer. Maria Theresa Knauth et al analyzed 68 published cases of an association of ITP with solid cancers (3).These authors observed that such cases occurred in variety of cancers. Such coexistence mostly occurred in breast and lung cancer patients; and very rarely in prostate cancer patients.ITP occurred in most of the patients concurrently (50%); about 5% of patients had ITP diagnosed prior to diagnosis of cancer and rest of patients had ITP diagnosed after being diagnosed a cancer. These authors observed that only few patients had complete response to ITP after surgical removal or chemotherapy of the cancer. Thus these authors suggested that in patients with ITP, a probability of cancer is always high. Further they propose that extensive search for a present or future cancer in such patients is not indicated, unless there are laboratories or clinical signs to suspect cancer. As far as treatment is concerned, for all patients with ITP who can be treated radically for cancer-treatment should and always be radical. Many authors have observed complete or partial remission of ITP after radical treatments. As far as palliative treatment is concerned it is appropriate to use protocols which have vincristine, cyclophosphamide, rituximab.

Many authors have suggested that although 80% of these ITP cases respond to prednisolone/ steroids; but sometimes other treatment modalities can also be effective. For example in patients with lymphomas – protocol CHOP (cyclophosphamide, doxorubicin , vincristine, Prednisolone) can be very effective protocol. Not only such protocols offer anti neoplastic therapy but also a very effective treatment for ITP. Ofcourse upon qualifying patients for such combination chemotherapies (4), one must weigh the short and long term risks versus benefits of the therapy (5) too presented cases of breast cancer with coexistent ITP and showed that safely we can administer adjuvant chemotherapy or adjuvant radiotherapy to breast cancer patients with co-existent ITP. These authors administered protocol AC (Doxorubicin, cyclophosphamide) and protocol FEC (5 Fluorouracil, epirubicine, and cyclophosphamide) as an adjuvant chemotherapy protocol among patients with breast cancers with coexistent ITP. They also demonstrated that safely adjuvant radiotherapy can be administered among such patients. As far as palliative chemotherapy and palliative radiotherapy is concerned , we have demonstrated in this case report that very safely we can administer palliative chemotherapy and palliative radiotherapy among patients with metastatic breast can with coexistent ITP.

## Discussion

Many patients with solid tumors are disqualified from potential curative or sometime palliative treatments with chemotherapy or radiotherapy due to coexisting thrombocytopenia. Globally many oncologists disqualify such patients too early without knowing the underlying cause of thrombocytopenia. Not every patient with thrombocytopenia is to be disqualified. As we have shown in this case report that many a times a patient with solid tumor can have coexistent ITP, which may be very well treated. And upon increasing platelet count, chemotherapy can be administered in such patients.

Many times oncologists treat breast cancer patients with coexistent thrombocytopenia only if they are ER, PR positive with hormonal therapies. Our patient too was treated with hormonotherapies –ie tamoxifen, aromatase inhibitors, exemestane , LHRH analogues , progestins (magetrol). But then we faced challenge when the patient became resistant to hormonal therapies initially (in 2014). At such moments oncologists should think about treating such patients with palliative chemotherapy protocols (if indicated).

It seems the problem is much bigger, as many of these patients with solid tumors never had bone marrow biopsy and thus never a work up of ITP is done. Thus as a result patient continues to have thrombocytopenia , and is unable to get potential therapies for example chemotherapy or radiotherapy. Such patients frequently die of bleeding complications. Furthermore, most of these solid tumor patients are transfused platelets, which cause further alloimmunisation causing production of further anti/ platelet antibodies and further destruction of existing platelets. Thus the severity of thrombocytopenia increases.

As indicated in most of the hematology textbooks, these patients should be administered glucocorticosteroids preferably encorton or intravenous immunoglobins as first line treatment of ITP. If patients develops steroid or immunoglobulin refractory ITP , then cyclophophamide , vincristine , danazol, rituximab, cyclosporine, azathioprine are some of the other potential therapeutic options .Splenectomy and newer drugs like TPO mimetics like romiplostin and eltrombopag are other options. Worth considering among such patients are chemotherapies that have cyclophosphmide, vincristine, etoposide, vinblastine, glucocorticosteroids.

## Conclusion

If thrombocytopenia coexists with cancer, then trephine biopsy is indicated to find the underlying cause of thrombocytopenia And if diagnosis of ITP is established, it seems that among such patients first ITP should be treated and upon achieving a satisfactory level of platelet count ( ie approx. 75 G/l ) certain chemotherapies can be carefully administered with dose modifications.

Patient disqualification for adjuvant or palliative chemotherapy (and /or radiotherapy), without having prior knowledge of underlying cause of thrombocytopenia is probably inappropriate. Thus knowledge of various diseases which cause thrombocytopenia and their treatments, say treatment of ITP in today's oncology practice is essential for every oncologist.

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