Bone Marrow Transplantation, (1999) 24, 335–337
© 1999 Stockton Press All rights reserved 0268–3369/99 $12.00
http://www.stockton-press.co.uk/bmt

Case report

Autoimmune thrombocytopenia in a patient with small cell lung cancer developing after chemotherapy and resolving following autologous peripheral blood stem cell transplantation

T Demirer[1], H Çelebi[1], M Arat[1], C Ustun[1], S Demirer[2], I Dilek[1], M Ozcan[1], O Ilhan[1], H Akan[1], G Gurman[1] and H Koç[1]

[1]*Dept of Hematology/Oncology and Bone Marrow Transplant Unit,* [2]*Dept of Surgery, Ankara University Medical School, Ibn-i Sina Hospital, Ankara, Turkey*

Summary:

A 46-year-old white male with small cell lung cancer (SCLC) limited to the thorax developed autoimmune thrombocytopenic purpura (AITP), following a cyclophosphamide, paclitaxel and G-CSF-containing regimen for peripheral blood stem cell (PBSC) mobilization. AITP associated with small or non-small cell lung cancer has been reported. We considered that the AITP in this case may be a part of paraneoplastic syndrome, which is frequently seen in patients with SCLC. The patient received HDC and autologous PBSC transplantation (APBSCT) for SCLC and the AITP resolved following transplantation, thus supporting the concept of HDC + APBSCT for the treatment of autoimmune diseases.

Keywords: autoimmune thrombocytopenia; small cell lung cancer; autologous peripheral blood stem cell transplantation

ITP is a well-known entity involving immune-mediated destruction of platelets. The majority of autoantibodies are of the IgG class and directed against the GPIIb/IIIa structural complex of the platelets.[1] Although in the majority of the cases a cause for the immune destruction and excess auto-antibody formation cannot be demonstrated, in some disorders such as rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, Graves disease, pernicious anemia, myasthenia gravis auto-antibodies have been documented. Immune thrombocytopenia is frequently encountered in lymphoproliferative disorders especially in non-Hodgkin's lymphomas and chronic lymphocytic leukemia.[1] In patients with lymphoproliferative and non-lymphoproliferative disorders, non-immune thrombocytopenia may appear in the context of concomitant chemotherapy or tumor infiltration of bone marrow preceding bone marrow failure.[1] AITP may also develop following autologous, allogeneic or syngeneic marrow or stem cell transplantation as an immunohematologic complication and may occur as early as the day of transplantation or as late as several years afterwards.[2]

Here we describe a case of AITP in a patient with SCLC, which developed after a cyclophosphamide and paclitaxel-containing chemotherapy regimen for PBSC mobilization and resolved following an APBSCT.

Case report

A 46-year-old white male was diagnosed with SCLC in March 1998. Staging work-up, including thoraco-abdominal computerized tomography (CT) and cranial CT was consistent with SCLC limited to thorax. CBC and serum biochemistry values were in the normal ranges before induction chemotherapy (WBC of 8×10^9/l, Hb of 14.4 g/dl and platelets of 254×10^9/l). The patient received cisplatin 60 mg/m^2/day i.v. on day 1 and etoposide 120 mg/m^2/day i.v. on days 1, 2 and 3 for three cycles. Before starting mobilization chemotherapy his WBC was 6.4×10^9/l, Hb 12.5 g/dl and platelets 232×10^9/l. For mobilization of stem cells he received cyclophosphamide (CY) 4 g/m^2/day i.v. $\times 1$ on day 1 and paclitaxel 200 mg/m^2/day i.v. $\times 1$ on day 2. On the fourth day of this regimen rhG-CSF (Neupogen, Amgen-Roche, Thousand Oaks, CA, USA) was given at a dose of 10 μg/kg/day i.v. twice daily until the end of PBSC collection. Following a nadir period in the early recovery phase (when the absolute neutrophil count reached $>1 \times 10^9$/l), PBSCs were collected with a continuous flow cell separator (Fenwall CS3000+, Baxter Healthcare Systems, Deerfield, IL, USA) for 3 consecutive days. The quantity of mononuclear and CD34$^+$ cells in the cryopreserved apheresis end-product were 3.7×10^8/kg and 4.9×10^6/kg, respectively. The patient was discharged with an Hb of 10.3 g/dl, Hct of 28.5%, WBC of 56×10^9/l and platelets of 100×10^9/l. After a 1-month rest period he was hospitalized for HDC and APBSCT. On this admission the platelet count was only 6×10^9/l, confirmed on blood smear examination. The other hematological parameters including coagulation profile were within normal ranges. Bone mar-

Correspondence: Dr T Demirer, Ankara University Medical School, Dept of Hematology/Oncology and Bone Marrow Transplant Unit, Ibn-i Sina Hospital, Sıhhıye 06100, Ankara, Turkey
Received 11 January 1998; accepted 23 March 1999

row aspiration and biopsy revealed a normocellular marrow with megakaryocytic overgrowth and no signs of neoplastic infiltration or myelodysplasia. Serum anti-platelet antibodies were positive on flow cytometric analysis. Laboratory work-up for isolated thrombocytopenia, consisting of viral, immunological and thyroid function tests was performed. Immunological tests including ASO, CRP, rheumatoid factor, anti-nuclear antibody and anti-double stranded DNA were all within normal limits. Therefore, the patient was diagnosed with AITP. Despite AITP, HDC + APBSCT was performed for the SCLC. Conditioning included thiotepa 250 mg/m^2/day i.v. on days −8, −7, melphalan 50 mg/m^2/day i.v. on days −6, −5, carboplatin 300 mg/m^2/day on days −4, −3 and −2. Day −1 was a rest day and following thawing, his autologous cryopreserved cells stored in the vapor phase of nitrogen at −165°C, were infused on day 0 without any complications. Twenty-four hours after autologous infusion rhG-CSF was started at a dose of 5 μg/kg/day i.v. until neutrophil recovery. An absolute neutrophil count of $>0.5 \times 10^9$/l and platelets of 20×10^9/l were present on days +10 and +12, post transplant, respectively. In the pre- and peri-transplant period 6 and 3 units of platelet concentrates from single donors were transfused. There was no excessive bleeding during the peri-transplant period. The patient was discharged on day +14 with an Hb of 10.3 g/dl, Hct of 35.5%, WBC of 8×10^9/l, and platelets of 66×10^9/l. On day +30, the platelet count reached 159×10^9/l and remained above 150×10^9/l on day +180. The patient was in complete remission from the SCLC on day +180 post transplant.

Discussion

Thrombocytopenia is caused by one of three mechanisms – decreased bone marrow production, increased splenic sequestration, or accelerated destruction of platelets.[1,3] Disorders that injure stem cells or prevent their proliferation in marrow frequently cause thrombocytopenia. They usually affect multiple hematopoietic cell lines so that thrombocytopenia is accompanied by varying degrees of anemia and leukopenia. The most common causes of decreased platelet production are marrow aplasia, fibrosis, or infiltration with malignant cells, all of which produce highly characteristic marrow abnormalities.[1,3,4] Splenic sequestration is one of the important causes of thrombocytopenia. Since one-third of the platelet mass is normally sequestrated in the spleen, splenectomy will increase the platelet count by 30%. In contrast, when the spleen enlarges, the fraction of sequestrated platelets increases, lowering the platelet count. Many patients with leukemia, lymphoma or a myeloproliferative syndrome have both marrow infiltration and splenomegaly and develop thrombocytopenia from a combination of impaired marrow production and splenic sequestration of platelets.[1] Accelerated platelet destruction may be due to either non-immunologic or immunologic factors. Abnormal vessels, fibrin thrombi, or intravascular prostheses can all shorten platelet survival and cause non-immunologic thrombocytopenia as is seen in patients with vasculitis, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura and disseminated intravascular coagulation. In addition, platelets coated with antibody, immune complexes, or complement are rapidly cleared by mononuclear phagocytes in the spleen or other tissues, inducing immunologic thrombocytopenia. The most common causes of immunologic thrombocytopenia are viral or bacterial infections, drugs, and a chronic autoimmune disorder referred to as ITP. Patients with immunologic thrombocytopenia do not usually have splenomegaly and have an active bone marrow with an increased number of megakaryocytes.[1,3,4]

Patients with SCLC have a wide spectrum of paraneoplastic syndromes such as secondary endocrinopathies, Guillian–Barre syndrome, neuropathies, retinopathies due to production of peptide hormones.[5] In this case, we could not exclude a paraneoplastic phenomenon. A literature search showed that lung cancer, either small cell or non-small cell, may be associated with AITP.[6–8] Therefore, we considered that the AITP in our patient may have been due to SCLC in which paraneoplastic syndromes are frequently seen. Autoimmune antibody formation due to paraneoplastic syndrome in a patient with SCLC is conceivable, and paraneoplastic syndrome in our patient may have triggered the formation of anti-platelet antibodies and as a result, AITP.

Intermediate high-dose CY has been used successfully for the treatment of refractory ITP.[9] CY + paclitaxel followed by rhG-CSF has been used previously for PBSC mobilization in many patients with breast and ovarian cancer and AITP or isolated thrombocytopenia was not reported in any of these cases.[10] It is interesting that in our case AITP developed following CY (4 g/m$^2 \times 1$) and a paclitaxel-containing regimen for PBSC mobilization and was not present before. Therefore, post-chemotherapy immunologic dysregulation may be a trigger for the development of AITP. Recently, Marmont *et al*[11] reported a case of refractory thrombocytopenic purpura of 10 years duration which did not respond to autologous, T cell-depleted marrow transplantation following conditioning with thiotepa and CY. Lim *et al*[12] reported two patients with refractory ITP treated with routine conditioning with CY 200 mg/kg over 4 days, and subsequently reinfused with their own mobilized PBSCs. Complete, steroid-independent platelet remission was obtained, but unfortunately both patients have subsequently relapsed after 12 and 18 months, respectively. One of the most interesting case reports of AITP is that of a patient whose donor had compensated AITP prior to the transplant, following which the recipient developed decompensated AITP post transplant.[13] This study suggested that the immune defect in autoimmune thrombocytopenia can be transferred in cells capable of proliferating in a bone marrow graft.[13] AITP in the current case resolved following HDC + APBSCT and the patient had stable platelet counts of over 150×10^9/l. APBSCT has been used for treatment of auto-immune diseases such as lupus, scleroderma and systemic sclerosis, and improvement in the clinical course following APBSCT in these patients has been reported by several authors.[14] Based on the literature, results of HDC + APBSCT for treatment of refractory ITP are not encouraging. Our case was not refractory ITP and it was associated with SCLC which may represent the clinical picture of paraneoplastic syndrome. Therefore, we do not suggest HDC + APBSCT for the treatment of the AITP but

disappearance of the AITP after APBSCT is interesting and supports the concept of HDC + APBSCT with or without stem cell manipulation for the treatment of auto-immune diseases.

References

1 Bussel JB. Autoimmune thrombocytopenic purpura. *Hematol Oncol Clin N Am* 1990; **4**: 179–191.
2 Klumpp TR. Immunohematologic complications of bone marrow transplantation. *Bone Marrow Transplant* 1991; **8**: 159–170.
3 Karpatkin S. Autoimmune (idiopathic) thrombocytopenic purpura. *Lancet* 1997; **349**: 1531–1536.
4 George JN, Woolf SH, Raskob GE *et al*. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood* 1996; **88**: 3–40.
5 Hinton RC. Paraneoplastic neurologic syndromes. *Hematol Oncol Clin N Am* 1996; **10**: 909–925.
6 Thuchishima S, Shimizu T, Yuasa K *et al*. Lung cancer surgery in a patient with idiopathic thrombocytopenic purpura. *Kyobu Geka* 1998; **51**: 424–427.
7 Ohura H, Sagawa M, Yoshida H *et al*. A case of idiopathic thrombocytopenic purpura combined with lung cancer. *Kyobu Geka* 1996; **49**: 484–486.
8 Tanita T, Nishimura T, Kubo H *et al*. A case of lung cancer combined with ocular myopathy and idiopathic thrombocytopenic purpura which was presumed to be caused by heart catheterization. *Kyobu Geka* 1994; **47**: 328–331.
9 McMillan R. Therapy for adults with refractory chronic immune thrombocytopenic purpura. *Ann Intern Med* 1997; **126**: 307–314.
10 Demirer R, Buckner D, Storer B *et al*. Effect of different chemotherapy regimens on peripheral-blood stem cell collections in patients with breast cancer receiving granulocyte colony-stimulating factor. *J Clin Oncol* 1997; **15**: 684–690.
11 Marmont AM, van Lint MT, Occhini D *et al*. Failure of autologous stem cell transplantation in refractory thrombocytopenic purpura. *Bone Marrow Transplant* 1998; **22**: 827–828.
12 Lim SH, Kell J, Al-Sabah A *et al*. Peripheral blood stem-cell transplantation for refractory autoimmune thrombocytopenic purpura. *Lancet* 1997; **340**: 475 (letter).
13 Minchinton RM, Waters AH, Kendra J *et al*. Autoimmune thrombocytopenia acquired from an allogeneic bone-marrow graft. *Lancet* 1982; **2**: 627–629.
14 Burt RK, Traynor AE, Pope R *et al*. Treatment of autoimmune disease by intense immunosuppressive conditioning and autologous hematopoietic stem cell transplantation. *Blood* 1998; **15**: 3505–3514.