

## Long Term Follow-up of Autologous Peripheral Blood Stem Cell transplantation in the treatment of a patient with acute panmyelosis with myelofibrosis

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Acute panmyelosis with myelofibrosis (APMF) is a rare haematological malignancy defined as subtype of acute myeloid leukaemia (AML) in the WHO classification of Tumours of haematopoietic tissue.<sup>1</sup> This disorder is an acute panmyeloid proliferation associated with fibrosis of bone marrow. Clinically it is characterised by little or no splenomegaly; Peripheral blood counts shows pancytopenia, few myeloblasts (<5%), a shift to the left with immature neutrophils and rare normoblasts, but no basophilia or monocytosis. No red cell morphological abnormality is observed.<sup>2,3,4</sup> Bone marrow histology shows various degrees of reticulin and collagen fibrosis. Haematopoietic tissue shows heterogeneity of cellularity. There is an increased number of immature trilineage haematopoietic elements and foci of blasts.<sup>5</sup> Currently, no standard therapy is available. APMF is reported to respond poorly to chemotherapy and to be associated with a short survival. According to a German report, median survival is 9 (range: 3-24) months.<sup>6</sup> Here we report a patient with APMF who achieved haematological remission after AML induction chemotherapy followed by autologous stem cell transplantation.

### Case report

In August 1997, a 56 years old man was admitted to our centre for anaemia and rapidly progressive thrombocytopenia. This patient had a history of traumatic pneumothorax, gastric ulcer and coronary heart disease successfully treated by percutaneous coronary angioplasty. For professional risks, he used to work in printing where he had been exposed to rubber solvents such as polyethane. On first examination there was no bleeding, no pallor, and the patient had no complain. Complete blood count was abnormal with haemoglobin 11,2 g/dL, white blood cell counts 5180/ $\mu$ l, platelets 46000/ $\mu$ l. There were circulating progenitor cells (4% metamyelocytes, 5% myelocytes and 1% blasts). Lactate dehydrogenase was increased (992UI/l, normal 160-480 U/l), and there were signs of iron overload (iron: 216  $\mu$ g/100 mL, normal 53-167  $\mu$ g/100 mL and ferritin 843ng/mL, normal 22-322 ng/mL). Marrow aspiration was a dry tap. Bone marrow biopsy showed severe osteomyelosclerosis but absence of blasts or neoplastic cells. Chest and abdominal CT scan were normal. Bone scintigraphy showed important and extensive activity. The patient was diagnosed as having idiopathic myelofibrosis. On Dupriez score he was in the low risk group. He received, as differentiating agents, 1-25 dihydroxy-vitamins D and androgens. One month later, the patient was readmitted to hospital for facial palsy. Physical examination showed right peripheral VII nerve palsy and disseminated cutaneous lesions. Those were multiple papules and plaques, various sized, located all over anterior trunk, back and limbs, cutaneous lesions were coloured in slight violet and pruritus free. There was no splenomegaly. Haemoglobin was 11,6 g/dL; platelets count 100000/ $\mu$ l, WBC 9460/ $\mu$ l with circulating progenitors (5% metamyelocytes, 6% myelocytes, 8% erythroblasts and 1% of blasts). LDH and alkaline phosphatase were increased (1496UI/l and 822 UI/l respectively). Once again, marrow aspiration was a failure, and no cytogenetic analysis could be performed. Bone mar-

**Figure 1.** Bone marrow biopsy shows hypocellular marrow.

**Figure 2.** Marked myelosclerosis.

**Figure 3.** Biopsy of cutaneous lesion shows massive infiltration of the dermis by blasts.

row biopsy showed marked osteomyelosclerosis (degree 3); haematopoietic tissue was hypocellular with dysplastic features and foci of blasts. The cutaneous lesions were biopsied and showed massive infiltration of the dermis by blasts positive for such a various myeloid and monocytic antigens (CD 68, CD43, muramidase and myeloperoxidase). The cerebrospinal fluid analysis showed increased proteins (156, normal: 15-40 mg/mL) with myeloid progenitor cells and erythroblasts. A diagnosis of leukemic transformation of the myelofibrosis was made. An induction treatment with Mitoxantrone; Etoposide; Cytarabine and intrathecal methotrexate administrations was performed. Five weeks after induction, right facial palsy disappeared. Cerebrospinal fluid was acellular. Bone marrow biopsy showed unchanged myelofibrosis (degree 3) with dysplastic megakaryocytes, but no blast

**Figure 4-5.** 8 months after autoSCT, bone marrow biopsy shows normocellular haematopoietic tissue, reduction of myelofibrosis and dysplastic megakaryocytes.

was observed. The patient received the first course of consolidation with high dose Cytarabine and Mitoxantrone. During haematological recovery, CD34 positive cells were collected. In December 1997, the patient underwent autologous stem cell transplantation (ASCT):  $8,5 \times 10^6$  CD34<sup>+</sup> cells/kg were reinfused after a conditioning regimen containing cyclophosphamide and TBI. Haematological reconstitution was obtained on day 18. White blood cells achieved 1000/ $\mu$ l with 550/ $\mu$ l ANC. Nevertheless, the patient needed platelet transfusions until 2 months after ASCT. Marrow biopsy performed one month after ASCT showed a reduction of the fibrosis, few megakaryocytes which had dysplastic features, and absence of blasts. Two months later, marrow aspiration confirmed the complete remission. Although myelofibrosis was dramatically reduced (degree 1), dysplastic megakaryocytes remained in the bone marrow biopsy. Eight years after ASCT, the patient developed a true myelodysplastic syndrome (Refractory anaemia). The trephine biopsy showed absence of fibrosis with hypercellular haematopoietic tissue, and blasts were less than 5%. No chromosomal abnormality was detected. The patient is currently treated with recombinant-EPO and G-CSF with partial response.

#### Discussion

The diagnosis of acute panmyelosis with myelofibrosis (APMF) is not always obvious. On basis of clinical, blood examination and bone marrow biopsy, the diagnosis of APMF can be retained: patients are mostly adult, and show signs of marked pancytopenia. There is no or little splenomegaly. Peripheral blood shows bone marrow failure with few myeloblasts (less than 5%), a shift to the left with immature myeloid cells, but no basophilia or monocytosis. Bone marrow biopsy shows various degrees of reticulin and collagen fibrosis. Haematopoietic cells present severe maturation defects of all three cell lineage (abnormalities concerning megakaryocytes are regularly observed). No specific chromosomal abnormalities characterize this disease. The prognosis is bad with a rapid progression to bone marrow insufficiency or development of acute myeloid leukaemia. Our patient showed a rapidly progressive anaemia and thrombocytopenia. White blood cell counts were normal, however circulating progenitor cells were present. The patient had no splenomegaly. Marrow biopsy showed reticulin and collagen fibrosis, lymphoid nodules, macrophages with hemosiderin deposits, increased number of microvessels but no cluster of blasts. Within two months, the patient met nearly all the criteria of APMF: he rapidly developed a leukaemic transformation with bicytopenia, immature haematopoietic elements and few blasts were observed on blood smear. Bone marrow was marked by myelosclerosis, dysplastic and blastic elements. Treatment of APMF is not standardised. Therapeutic strategies include sup-

portive treatment and a various cytoreductive agents in patients with evolving blast excess and overt AML.<sup>5</sup> In the present case, the patient was only 56 years old, and had a good performance status. We treated him as a leukemic transformation of myelofibrosis with induction and consolidation polychemotherapy followed by autologous stem cell transplantation. This treatment allowed a clinical and haematological remission during 7 years. To our knowledge this approach was never reported in APMF. The patient has now developed a true myelodysplastic syndrome (Refractory anaemia). This could be a relapse in another form of the disease. Indeed minor dysplastic features were present at diagnosis and persisted after treatment by AutoSCT. However several authors describe a higher incidence of secondary myelodysplasia after TBI.<sup>7,8,9</sup> This form of MDS appears 2-10 years after the treatment. Our patient could be developing this secondary form MDS but this can not be proven without specific cytogenetic abnormalities. The case reported here demonstrates that autologous stem cell transplantation can be successfully performed in patients with acute panmyelosis with myelofibrosis lacking a suitable donor for allogeneic stem cell transplantation. This treatment wasn't curative, but it allowed unexpected long term remission.

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#### References

1. Brunning RD, Matutes E, Flandrin G, et al. Acute myeloid leukaemia not otherwise categorized-acute panmyelosis with myelofibrosis. In: Jaffe ES, Harris NL, Stein H, Vardiman JW (eds). World Health Organization Classification of Tumours, Tumours of Haematopoietic and Lymphoid Tissues. IARC Press: Lyon, France, 2001, pp 103-104
2. Rojer R A, Mulder N H, Nieweg H O. Classic and acute myelofibrosis. A retrospective study. *Acta Haematol.*, 1978; 60: 108-116
3. Truong L D, Saleem A, Schwarz M R. Acute myelofibrosis. A report of four cases and review of the literature. *Medicine (Baltimore)*, 1984; 63: 182-187
4. Dzieciol J, Kemon A, Plonowski A, Sobaniec-Lotowska M, Sulkowski S, Musiatowicz B. Acute myelosclerosis-morphological and clinical analysis of the case. A review of literature. *Patol. Pol.*, 1992; 43: 189-191
5. Thiele J, Kvasnicka H M, Zerhusen G, Vardiman J, Diehl V, Luebbert M, Schmitt-Graeff A. Acute panmyelosis with myelofibrosis: a clinicopathological study on 46 patients including histochemistry of bone marrow biopsies and follow-up. *Ann Hematol*, 2004; 83: 513-521
6. Thiele J, Kvasnicka H M, Schmitt-Graeff A. Acute Panmyelosis with Myelofibrosis. *Leukemia & Lymphoma*, 2004; 45: 681-687
7. Brown JR, Yeckes H, Friedberg JW et al. Increasing incidence of late second malignancies after conditioning with cyclophosphamide and total-body irradiation and autologous bone marrow transplantation for NHL. *J Clin Oncol*, 2005; 23: 2208-2214
8. Hosing C, Munsell M, Yazji S and al. Risk of therapy-related myelodysplastic syndrome/acute leukaemia following high-dose therapy and autologous bone marrow transplantation for non-Hodgkin lymphoma. *Ann Oncol*, 2002; 13(3): 450-459
9. Metayer C, Curtis RE, Vose J, Sobocinski KA, Horowitz MM, Bhatia S, Fay JW, Freytes CO, Goldstein SC, Herzig RH, Keating A, Miller CB, Neville TJ, Pecora AL, Rizzo JD, Williams SF, Li CY, Travis LB, Weisdorf DJ. Myelodysplastic syndrome and acute myeloid leukaemia after auto transplantation for lymphoma: a multicenter case-control study. *Blood*, 2003; 101(5): 2015-2023