Acute transverse myelitis and autoimmune pancytopenia after unrelated hematopoietic cell transplantation

Immune-mediated reactions in allogeneic hematopoietic cell transplantation (HCT) may affect the nervous system causing myasthenia gravis, polymyositis and inflammatory demyelinating polyneuropathy[1] and the hematopoietic system causing autoimmune cytopenias.[2-5] We report a case of simultaneous acute transverse myelitis (ATM) and autoimmune pancytopenia (AIP) after an unrelated HCT successfully treated with immunosuppressive therapy.

A 21-year old male was diagnosed as having refractary anemia with excess of blasts and monosomy 7 in September 1996. He was referred to our institution in July 1997 for unrelated HLA-identical HCT. Conditioning was achieved with cyclophosphamide (60 mg/kg/day × 2 days) and unfractionated total body irradiation (1200 cGy). Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporin A (CyA) and a short course of three doses of methotrexate. Trilineage engraftment was achieved on day +25. Acute grade ++ skin GVHD (clinical I) was observed on day +30 and limited cutaneous chronic GVHD on day +120: both resolved with steroid treatment. Throughout this period hematologic parameters were within the normal range and the CyA was progressively tapered off.

In the 10th month after HCT and while receiving treatment with only CyA, the patient presented with fever, mucocutaneous purpura, jaundice and choluria. Physical examination revealed pallor, jaundice, hemorrhagic ulcerations on the oral mucosa and petechiae on the lower limbs. There were no evidence of chronic GVHD. Hematologic studies showed severe pancytopenia (hemoglobin: 99 g/L, white cell count 1.9×10^9/L, platelets 8×10^9/L) and a reticulocyte count of 18%. Serum biochemical investigation demonstrated hemolysis: bilirubin: 0.02 g/L, LDH 50 U/L, haptoglobin 0.084 g/L. The direct Coombs' test and indirect antiplatelet antibody test were positive. An antineutrophil antibody test was not conclusive. The remaining biochemical parameters were with the normal range and all other autoantibodies tested were negative. Bone marrow aspirate and trephine revealed normocellularity and erythroid hyperplasia without dysplastic features. Cytogenetic analysis showed a normal 46XY karyotype and chimerism studies revealed complete donor hematopoiesis. Multiple microbiological cultures, virological studies (CMV, Epstein-Barr, herpes simplex, varicella zoster, HIV-1, hepatitis B and C, parvovirus B19 and HTLV-1) and VDRL serology were negative.

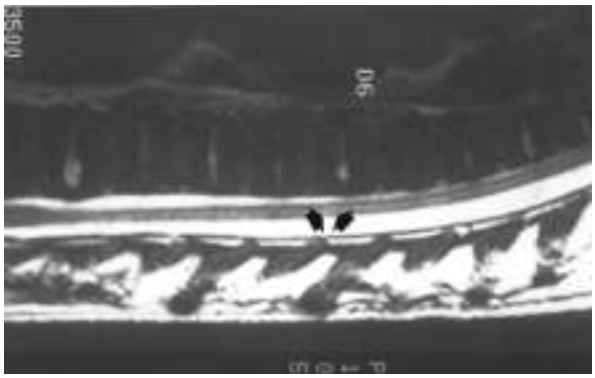

Figure 1. Hyperintense intramedullary lesion in T2 weighted images at the level of the T7 vertebral body.

Over the following days the patient developed paraparesis and sphincter control loss, without upper limb or cranial nerve symptoms. Neurological examination revealed weakness of the lower limbs with preserved tendon reflexes, and sensory loss below T7 including a decrease in propioceptive sensation. Neurophysiologic studies showed no peripheral nerve damage and normal somatosensory responses in the upper limbs. Somatosensory evoked potentials from the lower limbs were, however, of low amplitude and very slow. Cerebrospinal fluid studies were normal. Magnetic resonance imaging showed a hyperintense intramedullary lesion in T2-weighted images at the level of the T7 vertebral body (Figure 1).

A diagnosis of ATM with predominant involvement of the posterior spinal columns was made and therapy with immunoglobulin (0.4 g/kg/day × 5 days) and methylprednisolone (1 mg/kg/day) was started. After two weeks of treatment the neurological symptoms had disappeared and the pancytopenia had resolved: hemoglobin 137 g/L, white cell count 4.7×10^9/L, platelets 65×10^9/L.

Seven weeks later, when the steroid dose was being tapered off, the patient died of an infectious complication. The post-mortem revealed bilateral interstitial pneumonia caused by *Pneumocystis carinii* and CMV with adult respiratory distress syndrome (ARDS). Respiratory failure was the cause of death. The presence of hypercellularity with dysplastic features of the three hematologic lineages in the bone marrow was suspicious of a relapse of his myelodysplastic syndrome.

Table 1. Cases of autoimmune pancytopenia (AIP) reported in the literature. Case 4* only bicytopenia (anemia + thrombocytopenia).

Case(Ref)	Age/sex	Diagnosis	Pre-TX	T-cell depletion	Onset of AIP (months)	c- GVHD (at diagnosis of >AIP)	Autoimmune cytopenia	Therapy	Response and outcome.	Neurologic pathology
1(6)	47/F	CML	Cy/TBI	yes	+19	no	E+ N+ P-	steroids	CR	Yes (PN)
2(7)	17/M	SAA	Cy	no	+6	no	E+ N+ P+	Steroids, TLI	CR	no
3(8)	26/M	SAA	Cy/MoA	no	+10	no	E+ N+ P+	Steroids, splenectomy	PR, died by aspergillosis	no
4*(10)	40/M	SAA	Cy/TBI/ATG	no	+7	no	E+ N- P?	Steroids, splenectomy	PR	Yes (ATM)
Our case	21/M	MDS	Cy/TBI	no	+10	no	E+ NC P+	steroids	CR, died by sepsis.	Yes (ATM)

M: male, F: female, CML: chronic myeloid leukemia, SAA: severe aplastic anemia, MDS: myelodysplastic syndrome, PreTX:pretransplant conditioning, Cy: cyclophosphamide, MoA: monoclonal antibodies (Campath-1G), AIP: autoimmune pancytopenia,c-GvHD: chronic graft- versus-host-disease, E: anti-erythroid auto-antibodies; N: antineutrophil auto-antibodies; P: antiplatelet auto-antibodies; NC: not conclusive; TLI: total lymphoid irradiation, CR: complete response, PR: partial response, PN: peripheral neuropathy, ATM: acute transverse myelitis.

Delayed immune reconstitution, T-cell depletion, thymic damage, chronic GvHD and CyA therapy are well-known causes of multifactorial immune dysregulation after an HCT.

True autoimmune diseases after HCT are uncommon. Autoimmune thyroiditis, myasthenia gravis and isolated monocytopenias are the most frequently described.[2] AIP is exceptional and only three cases before this have been reported.[6-8]

As far as concerns the etiology of the pancytopenia, histologic, cytogenetic and chimerism bone marrow studies excluded graft rejection, poor engraftment, bone marrow aplasia by CMV or drugs and relapse as being responsible. The evidence in favor of an autoimmune origin includes the positive direct Coombs' and indirect anti-platelet tests as well as the rapid response to immunosuppressive therapy.

Immune-mediated reactions may also affect the nervous system causing myasthenia gravis, polymyositis and inflammatory demyelinating polyneuropathy.[1] ATM, to our knowledge, has been reported after HCT in only two patients.[9,10] We think it is possible to speculate that these patients had an autoimmune basis to their ATM as their clinical course parallelled the pancytopenia and they had an excellent response to steroids.

In summary, AIP is a life-threatening late complication of HCT frequently associated with other autoimmune phenomena. Preliminary analysis suggests a higher incidence of neurological pathologies in these cases (Table 1).

Rocío Pérez-Montes, Carlos Richard, Julio Baro, Julio Pascual, Rosario Varela,° Alberto Zubizarreta*

**Hematology and Neurology Department, Hospital Universitario Marqués de Valdecilla, Santander; °Hematology Department, Hospital Juan Canalejo, La Coruña. Spain*

Key words: Acute transverse myelitis; autoimmune pancytopenia; unrelated HCT.

Correspondence: Rocío Pérez-Montes, M.D., Servicio de Hematología, Hospital Universitario Marqués de Valdecilla, Avda. Valdecilla s/n. 39008, Santander, Spain. Phone: international +34-942-202573 - Fax: international +34-942-203450 - E-mail: hemala@humv.es

References

1. Openshaw H, Slatkin EN. Neurological Complications in Hematopoietic Cell Transplantation, 2nd edition. Thomas ED, Blume KG., Forman SJ, (Eds.), Blackwell Science Inc: MA: USA; 1999, pp. 659-73.
2. Sherer Y, Shoenfeld Y. Autoimmune diseases and autoimmunity post-bone marrow transplantation. Bone Marrow Transplant 1998; 22:873-81.
3. Klumpp TR. Immunohematologic complications of bone marrow transplantation. Bone Marrow Transplant 1991; 8: 159-70.
4. Klumpp TR, Block CC, Caligiuri MA, Rabinove SN, Soiffer RJ, Ritz J. Immune-mediated cytopenia following bone marrow transplantation. Case reports and review of the literature. Medicine (Baltimore) 1992; 71:73-83.
5. Rouquette-Gally AM, Boyeldieu D, Prost AC, Gluckman E. Autoimmunity after allogeneic bone marrow transplantation. A study of 53 long-term-surviving patients. Transplantation 1988; 46:238-40.
6. Klumpp TR, Caligiuri MA, Rabinowe SN, et al. Autoimmune pancytopenia following allogeneic bone marrow transplantation. Bone Marrow Transplant 1990; 6:445-7.
7. Bashey A, Owen I, Lucas GF, et al. Late onset immune pancytopenia following bone marrow transplantation. Br J Haematol 1991; 78:268-74.
8. De Lord C, Marsh JC, Smith JG, Singer CR, Gordon-Smith EC. Fatal autoimmune pancytopenia following bone marrow transplantation for aplastic anaemia. Bone Marrow Transplant 1996; 18:237-9.
9. Drobyski WR, Potluri J, Sauer D, Gottschall JL. Autoimmune hemolytic anemia following T-cell-depleted allogeneic bone marrow transplantation. Bone Marrow Transplant 1996; 17: 1093-9.
10. Richard S, Fruchtman S, Scigliano E, Skerrett D, Najfeld V, Isola L. An immunological syndrome featuring transverse myelitis, Evans syndrome and pulmonary infiltrates after unrelated bone marrow transplant in a patient with severe aplastic anemia. Bone Marrow Transplant 2000; 26:1225-8.