

Takayasu's arteritis secondary to myelodysplasia as a predictor of poor outcome: Two case reports

C. Amberger¹, C. Denzlinger³,
J. Janzen², M. Müller-Schimpfle⁴, M. Mohren¹,
I. Kötter¹

¹Department of Medicine II and ²Department of Pathology of the Tübingen University Hospital; ³Department of Medicine III, Marienhospital, Stuttgart; ⁴Department of Radiology, Städtische Kliniken Frankfurt Hoechst, Frankfurt, Germany.

Christopher Amberger, MD; Claudio Denzlinger, MD; Jan Janzen, MD; Markus Müller-Schimpfle, MD; Martin Mohren, MD; and Ina Kötter, MD.

Please address correspondence to:
Ina Kötter, MD, Department of Medicine II, University Hospital of Tübingen, Otfried-Müller-Strasse 10, D-72076 Tübingen, Germany.

E-mail: ina.koetter@med.uni-tuebingen.de

Received on March 3, 2003; accepted in revised form on February 19, 2004.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2004.

Key words: Myelodysplasia, Takayasu's arteritis, vasculitis, chronic myelo-monocytotic leukaemia.

ABSTRACT

We present two patients with myelodysplasia in association with Takayasu's arteritis (TA). In both patients intensive immunosuppressive treatment could not control the vascular inflammation. Subsequently both patients developed myelodysplasia, rapidly progressing to secondary acute myelogenous leukaemia. One patient had a peripheral blood stem cell transplant from a compatible sibling donor, but died of refractory leukaemia 5 months later. The other patient died of fungal sepsis. These are the first two patients reported to have TA associated with myelodysplasia/secondary leukaemia.

Introduction

About 10% of patients with myelodysplastic syndromes (MDS) concomitantly have autoimmune phenomena. Cutaneous leukocytoclastic vasculitis and arthritis are the most common manifestations (1-4). Paraneoplastic inflammation of the larger vessels including the cranial arteries has been observed, albeit rarely, in MDS (5, 6) but involvement of the aorta fulfilling the ACR classification criteria for Takayasu's arteritis (TA) (7) has never been described until now. We report on two patients with MDS associated with large vessel arteritis which could be classified as TA.

Case 1

A 50-year-old previously healthy woman presented with fever, intermittent arthralgia, retrosternal pain, vertigo, panuveitis of the left eye, ipsilateral tinnitus and slight signs of left-sided Bell's palsy. Carotids were tender to palpation and there were bruits over the carotid and subclavian arteries. Movement provoked pain in the upper and lower limbs. Pulses were regular and the blood pressure was equal in both arms.

Laboratory investigation revealed monocytosis ($3,500/\text{mm}^3$), anaemia (haemoglobin 10.3 g/dL), and mild thrombocytopenia ($116,000/\text{mm}^3$). The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and IL-6 were elevated (63/107, 20.12 mg/dL, and 1.38 ng/dL, respectively) in the absence of any evidence of an acute infection. Autoantibody testing was negative and com-

plement components were within the normal range.

Magnetic resonance imaging (MRI) demonstrated circular thickening of the thoracic aorta and of all supraortic branches (Fig.1). Perfusion of the left lung was markedly decreased.

According to the ACR classification criteria (7), the patient's clinical and MRI findings were consistent with TA. Immunosuppressive treatment with prednisolone, azathioprine, cyclophosphamide and cyclosporine was ineffective. Only high-dose steroids (500 mg prednisolone daily for 3 days) resulted in short-term control of the symptoms. Monocytosis persisted and blasts were detected in the peripheral blood. Bone marrow analysis revealed a hypercellular marrow with 24% monoblasts, dysplastic erythropoiesis and complex cytogenetic aberrations (46, XX, del(5)(q13q33); 43-45, XX, inv(3)(q21q26), del(5)(q13q33), -7, add(12), -16, -18, -20, + mar) consistent with the transition of CMML into secondary acute myelogenous leukaemia (sAML).

Peripheral blood stem cell transplantation was performed from an HLA-identical sibling donor followed by intensive immunosuppression with cyclosporine, prednisolone and mycophenolate-mofetil. The vasculitis resolved, but the patient died of persistent leukaemia 5 months later. An autopsy was not performed.

Case 2

A 40-year-old woman with systemic lupus erythematosus (SLE) was admitted with fever, neck pain and sore throat. Her carotids were tender to palpation and the carotid pulses were weak. Laboratory testing showed normocytic anaemia (Hb7.6g/dL) and marked thrombocytopenia ($36,000/\mu\text{L}$). The ESR, fibrinogen and CRP were elevated indicating systemic inflammation (53/84, > 1100 mg/dL, 15.37 mg/dL). Serum creatinine was elevated corresponding to a creatinine clearance of 60 mL/min. The patient had undergone a kidney transplant 13 years ago because of lupus nephritis and had been taking prednisolone and cyclosporine for immunosuppression since then. In addition, she had repeatedly been treated with cyclophos-

phamide. The clinical course was characterized by increasing cervical pain and by the occurrence of retrosternal burning pain refractory to analgesics including morphine. Diagnostic imaging with MRI showed thickening of the wall of both common carotid arteries and their branches; digital subtraction angiography demonstrated only minor stenosis of the proximal right vertebral artery.

Despite intensive diagnostic efforts we detected no signs of infection or lupus activity. TA was diagnosed on the basis of the findings mentioned above. In spite of intensified immunosuppression (2 x 2 g cyclophosphamide i.v., prednisolone, cyclosporine) and antimicrobial treatment, the cervical pain, fever and systemic inflammation considerably worsened. Bone marrow analysis showed marked dysplasia of the granulopoiesis and erythropoiesis with 20% myeloblasts consistent with a refractory anaemia, with excess blasts in transformation (RAEB-t).

The patient developed progressive dyspnea, tachycardia with a falling blood pressure and died of multiple organ failure. On post mortem examination multiple infarctions were found in both lungs and mycotic septic emboli were detected in the larynx, oesophagus and stomach. Acute right heart failure was diagnosed as the cause of death. Histological sections of the common carotid arteries and the aortic arch showed severe fibrosis localized in the outer parts of the media and in the adventitia. Some of the elastic fibers were destroyed and had been replaced by fibrous tissue. Furthermore rare mononuclear inflammatory cells and neovascularised areas were noted (Fig. 2).

Discussion

MDS is a clonal disease of the haematologic stem cells. Dysplasia of the haematopoietic cells and an increased percentage of myeloblasts represent typical morphologic changes in the bone marrow and are used to divide the disease in five subgroups (8-10). Numeric and structural cytogenetic abnormalities in the marrow cells are seen in 40-60% of *de novo* MDS cases. Complex cytogenetic aberrations, such as those observed in patient 1 correlate with a

Fig. 1. MR imaging of the thoracic vessels. Axial T1-weighted fat-saturated sequence after the administration of contrast medium (Gd-DTPA 0.1 mmol/kg b.w.). Notice the marked concentric thickening of the aortic wall at the level of the aortic arch, descending aorta, azygos vein (1 and 2) and pulmonary artery bifurcation (2).



more aggressive disease. Extensive cytotoxic treatment (e.g. cyclophosphamide) can lead to treatment-related MDS which has a poor prognosis as well. Patient 2 had received cyclophosphamide several times, but the cumulative dose was not high enough to raise the suspicion of a connection between the administration of cyclophosphamide and the development of MDS.

Immune-mediated complications, e.g. rheumatic diseases and systemic vasculitides, in MDS patients are not uncommon and occur in about 10% (2). A prospective study by Hamidou *et al.* showed a prevalence of 18% of polymyalgia rheumatica and polyarteritis nodosa-type systemic vasculitis in MDS patients (11). The literature includes case reports on polyarteritis nodosa (PAN), Henoch-Schönlein purpura, polymyalgia rheu-

matica, leukocytoclastic vasculitis, Wegener's granulomatosis, aortitis, Behçet's disease, relapsing polychondritis and unclassified forms in association with MDS (5, 11-17).

Our patients represent the first two case reports of an association of MDS and Takayasu's disease. Uveitis and involvement of the pulmonary artery are common in TA. Histological findings reveal a granulomatous giant cell arteritis in the acute state, whereas fibrotic changes are seen in the chronic state.

SLE, therapy with corticosteroids and kidney transplantation are risk factors for atherosclerosis. Nevertheless, patient 2 had severe cervical pain located in both carotids and MRI of the neck showed enhancement after the application of contrast media as well as inflammatory edema, which is extremely unusual for

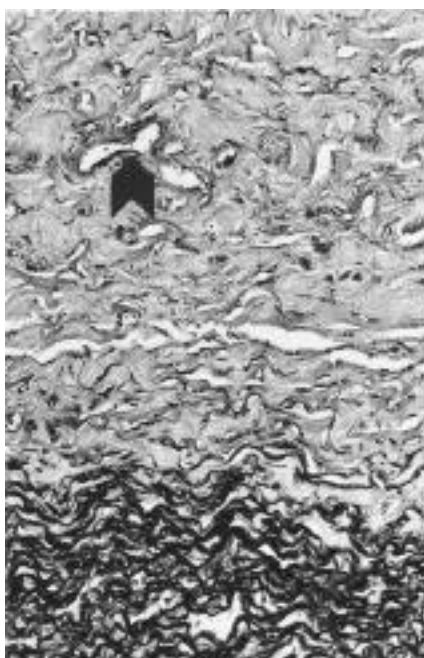


Fig. 2. Histology of the right common carotid artery. The outer part of the media and adventitia present severe fibrosis incorporating the nerves and vasa vasorum. There are rare mononuclear inflammatory cells and neovascularized areas (arrow) in the adventitia. (Van Gieson-stain, x 200)

atherosclerosis but typical for TA. Furthermore the histological findings in patient 2 – fibrosis in the outer parts of the media and in the adventitia of the affected common carotid arteries and the aortic arch – are considered to be a consequence of the inflammatory process and are compatible with the typical chronic lesions of TA (8-11). There were only slight atherosclerotic changes in the thoracic and abdominal aorta. Although the pathophysiology of the relationship between MDS and autoimmunity is not well understood, it is reasonable to suspect a causal relationship rather than to assume a random coincidence of TA and MDS. Abnormal monocytic activity in CMML with increased secretion of inflammatory cytokines seems to have a special impact on the pathogenesis in MDS-associated vasculitis (15,22). However, cytokine measurements in patient 1 revealed only a moderate elevation of IL-6. Another hypothesis suggests that dysregulation of T- or B-cell function in MDS (e.g., the polyclonal activation of B cells, reduced number of CD4 T cells and NK

cells, clonal CD5 positive B cell populations) might lead to autoimmune phenomena (3, 15).

Primary TA in general responds well to immunosuppressive treatment. This did not hold true for our patients. Immunosuppressive treatment allows only short-lived control of the secondary rheumatic syndromes associated with MDS, and patients with MDS and paraneoplastic autoimmune syndromes are generally young and have a poorer prognosis (2, 8, 9). Thus, in autoimmune diseases secondary to MDS, more aggressive treatment strategies should be considered. MDS is potentially curable by intensive chemotherapy and stem cell transplantation. However, in patient 1 allogeneic transplantation together with intensive immunosuppression resulted in resolution of the vasculitis but could not eliminate the sAML. The association of vasculitis mimicking TA with haematological diseases appears to predict a very poor outcome for the underlying malignancy.

References

- CASTRO M, CONN DL, SU WPD, GARTONJP: Rheumatic manifestations in myelodysplastic syndromes. *J Rheumatol* 1991; 18: 721-7.
- BILLSTRÖM R, JOHANSSON H, JOHANSSON B, MITELMAN FN: Immune-mediated complications in patients with myelodysplastic syndromes - clinical and cytogenetic features. *Eur J Haem* 1995; 55: 142-8.
- ENRIGHT H, MILLER W: Autoimmune phenomena in patients with myelodysplastic syndromes. *Leuk Lymphoma* 1997; 24: 483-9.
- PIRAYESH A, VERBUNT RJ, KLUIN PHM, MEINDERS AM, DE MEIJER PH: Myelodysplastic syndromes with vasculitic manifestations. *J Intern Med* 1997; 242: 425-31.
- KOHLI M, BENNETT RM: An association of polymyalgia rheumatica and myelodysplastic syndromes. *J Rheumatol* 1996; 21: 1357-9.
- ESPINOSA G, FONT J, MUNOZ-RODRIGUEZ FJ, CERVERA R, INGELMO M: Myelodysplastic and myeloproliferative syndromes associated with giant cell arteritis and polymyalgia rheumatica: A coincidental coexistence or a causal relationship? *Clin Rheumatol* 2002; 21: 309-13.
- AREND WP, MICHEL BA, BLOCH DA *et al.*: The American College of Rheumatology: criteria for the classification of Takayasu's arteritis. *Arthritis Rheum* 1990; 33: 1129-34.
- DANLEY R: Myelodysplasia. *Curr Opin On - col* 2000; 12: 13-21.
- GREENBERG PL: Myelodysplastic syndromes. In HOFFMAN R, BENZ EJ, SHATTIL SJ, FURIE B, COHEN HJ, SILBERSTEIN LE and MCGLAVER P (Eds.): *Hematology - Basic Principles and Practice*, 3rd ed., Churchill Livingstone 2000: 1106-29.
- BENNETT JM, CATOVSKY D, DANIEL MT, FLANDRIN G, GALTON DAJ, GRALNICK HR and SULTAN C, and the FRENCH-AMERICAN-BRITISH CO-OPERATIVE GROUP: Proposal for the classification of the myelodysplastic syndromes. *Br J Haematol* 1982; 51: 189-99.
- HAMIDOU MA, DERENNE S, AUDRAIN MAP, BERTHELOT JM, BOUMALASSA A, GROLLEAU JY: Prevalence of rheumatic manifestations and antineutrophil cytoplasmic antibodies in haematological malignancies. A prospective study. *Rheumatology* 2000; 39: 417-20.
- BLANCO R, GONZALEZ-GAY MA, IBANEZ D, LOPEZ-VIANA A, FERRAN C, REGUEIRA A, GONZALEZ-VELA C: Henoch-Schönlein purpura as clinical presentation of a myelodysplastic syndrome. *Clin Rheumatol* 1997; 16: 626-8.
- TAILLAN B, FERRARI E, GARNIER G, FUZIBET JG, DUJARDIN P: Association maladie de Wegener et syndrome myelodysplasique. *Ann Med Interne (Paris)* 1992; 143: 478-9.
- DIEBOLD J, RAUTH G, JÄGER K, LÖHRS U: Bone marrow pathology in relapsing poly-chondritis: high frequency of myelodysplastic syndromes. *Br J Haematol* 1995; 89: 820-30.
- HAMIDOU MA, BOUMALASSA A, LAROCHE C, EL KOURI D, BLETRY O, GROLLEAU JY: Systemic medium-sized vessel vasculitis associated with chronic myelomonocytic leukaemia. *Semin Arthritis Rheum* 2001; 31: 119-26.
- KIMURA S, KURODA J, AKAOGI T, HAYASHI H, KOBAYASHI Y, KONDO M: Trisomy 8 involved in myelodysplastic syndromes as a risk factor for intestinal ulcers and thrombosis – Behçet's syndrome. *Leuk Lymphoma* 2001; 42: 115-21.
- LOPEZ FF, VAIDYAN PB, MEGAAE, SCHIFFMAN FJ: Aortitis as a manifestation of myelodysplastic syndrome. *Postgrad Med J* 2001; 77: 116-8.
- JANZEN J, VUONG PN, ROTHENBERGER-JANZEN K: Takayasu's arteritis and fibromuscular dysplasia as causes of acquired atypical coarctation of the aorta: retrospective analysis of seven cases. *Heart Vessels* 1999; 14: 277-82.
- LAGNEAU P, MICHEL JB, VUONG PN: Surgical treatment of Takayasu's disease. *Ann Surg* 1987; 205: 157-266.
- VIRMANI R, LANDE A, MCALLISTER HA JR: Pathological aspects of Takayasu's arteritis. In LANDE A, BERKMEN YM and MCALLISTER HA (Eds.): *Aortitis: Clinical, Pathologic and Radiographic Aspects*, New York, Raven Press, 1986.
- NASU T: Takayasu's trunco-arteritis. Pulseless disease or aortitis syndrome. *Acta Pathol Jpn* 1982; 32: 117-31.
- SHETTY V, ALLAMPALLAM K, RAZA A: Increased macrophages, high serum M-CSF and low serum cholesterol in myelodysplasia and Kawasaki disease. *Br J Haematol* 1999; 106: 1068.