Microscopic polyangiitis diagnosed at hysterectomy

J.T. Gran1, Aa. Berner2, A. Kloster-Jensen3, L. Bostad4

1Department of Rheumatology University Hospital of Tromsø, Tromsø; 2Department of Pathology, The National Hospital for Cancer, Radiumhospital, Oslo; 3Department of Gynecology and Obstetrics, Central Hospital of Aust Agder, Arendal; 4Department of Pathology, The Gade Institute, Haukeland Hospital, Bergen, Norway.

ABSTRACT
A 78 year old female developed polyneuropathy, weight loss, malaise, and joint pain. Necrotizing vasculitis was diagnosed at hysterectomy, and later renal biopsy demonstrated focal segmental necrotizing glomerulonephritis. The pathological findings together with the presence of pANCA was consistent with a diagnosis of microscopic polyangiitis (MPA). This is the first clinical description of MPA with involvement of the uterus.

Introduction
Among the vasculitides, the term microscopic polyangiitis (MPA) is preferably reserved for patients with small vessel vasculitis associated with rapidly progressive focal segmental necrotizing glomerulonephritis (1). It is not included in the American College of Rheumatology (ACR) classification criteria for vasculitides (2), but has been defined as a separate clinical entity by the Chapel Hill Conference consensus criteria (3). The etiology remains unknown. The diagnosis of MPA may be difficult and easily confused with both polyarteritis nodosa (PAN) and Wegener’s granulomatosis (WG). In addition to glomerulonephritis, the major clinical manifestations of MPA encompass weight loss, arthralgia, myalgia, purpura, mononeuropathies, and hemophthisis (4-6). The disease may, however, develop in almost any organ. To our knowledge, involvement of the uterus has not been reported previously. We therefore wish to report a patient who was fortuitously diagnosed as having MPA after a histological examination of a resected uterus.

Case report
A white female 78 years of age was referred with a six-month history of pain in the wrists, ankles, toes and adjacent musculature. She had a two-week history of declining general health, night sweats and loss of sensation in the legs. Two days prior to admission, she noted increasing numbness of the left distal arm.

She was admitted to hospital on February 8, 1993. A slight fever was noticed (38.0°C). Reflexes were absent in the legs, and she was unable to stand on her feet. Arthritis was found in the right wrist only. Haemoglobin was 11.9 g/dl, ESR 41 mm/hour, CRP 138 mg/l, white blood cell count 16.0 x 10⁹/l, thrombocytes 310 x 10⁹/l, serum calcium 2.20 mmol/l, serum iron 2 µmol/l, TIBC 33 µmol/l, ferritin 735 µg/l (normal 10 -200), serum albumin 25 g/l, and ASAT 79 U/l (normal 10 -35), ALAT 87 U/l (normal 10 -35) and GT 58 U/l (normal 5 -54). Serum rheumatoid factors (Waaler’s test) were present at titers of 128. Urine contained several hyaline and cellular casts, and the amount of proteinuria was estimated to be 0.3 g/l.

The following laboratory tests were all within normal limits: red blood cells, differential white blood cell count, reticulocytes, creatinine, serum potassium, creatine kinase, serum and spinal electrophoresis, immunoglobulins G, M and A, circulating immune complexes (C1q test), anti-nuclear antibodies, anti-neutrophilic cytoplasmic antibodies, antibodies against hepatitis A, B and C, Wasserman’s test, antibodies against Borrelia burgdorferi and cytomegalovirus, blood cultures, and bone marrow aspiration. X-rays of the lungs and heart and ultrasound of the abdomen revealed normal findings.

Nerve conduction studies showed signs of peripheral neurogenic lesions, and no motoric or sensoric responses were recorded in the lower extremities. A lumbar puncture revealed white blood cells 25 mega/l, total protein 0.29 g/l, and glucose 3.7 mmol/l.

Malignancy was suspected, and a routine gynecological examination disclosed a slightly enlarged uterus. Ultrasoundography showed a possible tumor, located in the midline, size 3-4 cm. Both biopsy and cytology suggested adenocarcinoma. On March 13, the uterus and both ovaries were surgically removed. Pathological examination of the resected uterus disclosed an endometrial carcinoma which was histologically classified as a highly differentiated adenocarcinoma of the endometroid type without deep infiltration. In addition, necrotizing arteritis of several small to medium-sized arteries in the uterus, tubes and ovaries were disclosed (Fig. 1). Abdominal angiography, including mesentric and renal arteries showed normal findings.
The patient’s general health deteriorated rapidly, and she was now bedridden with total loss of appetite and weight loss of more than 10 kg since the onset of her disease. On April 1 treatment with intravenous cyclophosphamide (CyP) 500 mg and corticosteroids was initiated. Vaginal selecron was given 4 times as treatment for her uterine adenocarcinoma. After 5 i.v. pulses of CyP administered every second week, the patient reported significant improvement. Monthly pulses were then given for 4 months. The intervals were gradually increased so that by March 1997 pulses were administered every 5 months. In 1997, it was decided to lengthen the intervals to every 6 months.

In October 1997 the patient complained of malaise, but clinical examinations revealed normal findings. Her creatinine was 83. She was again admitted to hospital in November 1997 due to increasing dyspnea. However, clinical examination and radiology provided no evidence of ongoing pulmonary disease. A routine urine analysis revealed pronounced hematuria, proteinuria and leukocyturia. In January 1998, granular casts were found, and the creatinine had risen to 383. Creatinine clearance was 10 ml/min. Urine protein was estimated to 5.3 g/l, ANCA was positive at titers of 64 units, determined as pANCA, while c-ANCA was negative. The ESR was 90, WBC 8.5, and Hb 6.8.

A renal biopsy showed 17 glomeruli, 6 of which demonstrated advanced glomerular sclerosis with fibrous crescents. Some glomeruli with fibrocellular crescents and necrosis were also detectable (Fig. 2). Tubulointerstitial fibrosis was present. Convincing vasculitis was not seen. The findings were interpreted as focal necrotizing glomerulonephritis with both chronic and acute lesions consistent with MPA.

Three pulses of methylprednisolone (19 each) were administered on three consecutive days, followed by CyP 500 mg weekly. Oral corticosteroids (Prednisolone) 50 mg initially and then in tapering doses were also given. The patient was last seen on March 4 and her condition had already improved. The serum creatinine was now 270.

Discussion

Our patient was a 78 year old female whose clinical manifestations consisted of arthralgia, monoarthritis, myalgia, fever, declining general health, night sweats, weight loss and loss of sensation in the lower extremities. Examination revealed elevated ESR, CRP, leukocytosis, pronounced peripheral polyneuropathy, and urine analysis compatible with nephritis. Histological examination of a resected uterus showed necrotizing arteritis and localized endometrial adenocarcinoma. The latter finding was regarded as a coincidental finding in a patient aged 78 years. Moreover, the clinical course of the systemic vasculitis with recurrence of vasculitic manifestations did not support an association between cancer and vasculitis. A comprehensive search for other malignant diseases and systemic connective tissue disorders was unsuccessful.

Although abdominal angiography and serological tests for hepatitis B surface antigen were both negative, the clinical and pathological findings were initially interpreted as being consistent with PAN. According to current classification criteria (2), weight loss, myalgias, neuropathy, and histological evidence of arteritis are sufficient evidence to classify a patient as having PAN. Moreover, polyneuritis was a predominant clinical feature which further supported a diagnosis of PAN (7). The absence of pulmonary manifestations and the lack of detectable cANCA made a diagnosis of WG unlikely.

Based on examination of the urine sediments, however, the patient also had evidence of nephritis, suggesting a diagnosis of MPA to be more likely than PAN. Five years later, during a severe exacerbation with deteriorating renal function, a biopsy specimen showing necrotizing glomerulonephritis with crescents finally established the diagnosis of MPA. The patient had now also developed pANCA, further substantiating MPA as the most likely diagnosis. Unfortunately, we did not have the opportunity to perform tests

Fig. 1. Necrotizing vasculitis of the uterus.

Fig. 2. Renal biopsy. Glomerulus with fibrocellular crescent (arrow) and an area with segmental necrosis (short arrow) H & E x 400.
for the determinations of anti-Pr3 and anti-MPO, but the possible presence of the latter would have strongly suggested a diagnosis of MPA.

We are not aware of any case report of MPA describing involvement of the uterus as part of the clinical picture. In a report of 15 patients with vasculitis affecting the kidneys who were subjected to autopsy, however, Serra and co-workers (8) found vasculitic lesions confined to the uterus in one case. Unfortunately, a comprehensive clinical description of the case was not provided. However, it is possible that some previously reported cases exhibiting uterine involvement have been classified as PAN, especially prior to the promulgation of the Chapel Hill consensus which established MPA as a distinct clinical entity. For example, in the reports of Piette and co-workers (10) and of Möller and co-workers (11), the clinical and laboratory data presented offered no possibility of distinguishing between PAN and MPA. Thus, the present report is most likely the first clinical description of uterine involvement in MPA, in which the diagnosis has been rather firmly established.

In PAN, however, involvement of the uterus has been reported previously. Patalano and Sommers (9) in a series of 17 females subjected to autopsy, found vasculitic lesions in the uterus in 6 (35.3%) cases. Furthermore, case reports of patients with PAN diagnosed at hysterectomy have also been presented (10, 11). Typically, the two patients reported responded to immunosuppressive treatment with complete remission in both cases. The present patient also responded to treatment with corticosteroids and CyP, but when the intervals were increased to more than 5 months, exacerbations of the disease manifestations occurred. The recurrence was characterized by deteriorating renal function. Contrary to PAN, which is often considered “a one shot disease”, MPA is characterized by disease recurrences (12), and the outcome of MPA is often regarded as being more severe than that of PAN (13). The mortality rate in full-blown MPA is high (4, 13, 14), a frequent cause of death being respiratory involvement (15).

Although MPA diagnosed at hysterectomy may appear to be a rare event in everyday clinical medicine, the severity of the disease and the need for an early diagnosis to initiate immunosuppressive therapy emphasize the importance of clinical awareness of the possibility of MPA in cases presenting with general symptoms, either alone or in combination with progressive polyneuropathy. In patients with vasculitis fortuitously diagnosed by hysterectomy, other vasculitides such as giant cell arteritis (16) and Wegener’s granulomatosis (17) should also be considered.

References
4. SAVAGE CO, WINEARLE CG, EVANS DJ, REES AJ, LOCKWOOD CM: Microscopic polyarteritis: presentation, pathology, and prog-