Acute enlargement and subsequent rupture of an abdominal aortic aneurysm in a patient receiving chemotherapy for pancreatic carcinoma

Stefan J. Palm, MD, Georg P. Russwurm, MD, David Chang, MD, Alla M. Rozenblit, MD, Takao Ohki, MD, and Frank J. Veith, MD, *New York, NY, and Cologne, Germany*

We report a case of ruptured abdominal aortic aneurysm (AAA) in a patient receiving chemotherapy for pancreatic cancer. We reviewed the literature on the effects of corticosteroids and chemotherapy on AAA formation and discuss possible mechanisms for drug action to promote aneurysm expansion and rupture. If cancer and AAA coincide and curative chemotherapy is possible, a potential impact of chemotherapy on AAA expansion should be considered. (J Vasc Surg 2000;32:197-200.)

Various predictors for an increased risk of abdominal aortic aneurysm (AAA) rupture are known, such as aneurysm size and growth rate, smoking, chronic obstructive pulmonary disease (COPD) and hypertension.[1-4] A promoting effect of prolonged corticosteroid treatment on aneurysm growth has been suggested[1,5-10]; however, an association between chemotherapy and AAA expansion has not yet been established. We report a case of AAA rapid growth and rupture in a 73-year-old man who received chemotherapy with gemcitabine, cisplatinum, prednisone, and dexamethasone for metastatic pancreatic carcinoma.

CASE REPORT

In December 1997, a 73-year-old normotensive male physician had a palpable pulsatile mass in the lower abdomen and a 6-week history of lower back pain. His medical history was significant for polymyalgia rheumatica. The patient had normal blood cholesterol levels, was a nonsmoker, and did not drink alcohol. Of note was that his mother died of pancreatic cancer at the age of 70 years. On physical examination, blood pressure was 120/70 with a heart rate of 80 beats per minute. There was a palpable pulsatile mass in the lower abdomen. The remainder of the physical examination was normal, including the pulses at all levels. Results from all laboratory tests were normal. A contrast enhanced computed tomography (CT) scan revealed an AAA of 5.8 cm in largest diameter (Figs 1 and 2, *A*) and bilateral iliac artery aneurysms. Additionally, a 1.5-cm mass was present in the tail of the pancreas. In January 1998, an open AAA repair with removal of the pancreatic tail mass was planned. Endovascular aneurysm repair was not attempted because of the anatomy of the bilateral iliac aneurysms and the need for exploration of the pancreatic mass. During surgery there was gross evidence of metastatic disease. Biopsies of the hepatic lesions confirmed a metastatic adenocarcinoma of primary pancreatic origin. Because there was no evidence of an impending AAA rupture, neither AAA repair nor removal of the pancreatic tail mass was performed. A pancreatic tumor and multiple liver lesions up to 1.2 cm in size were demonstrated in a subsequent CT scan in March 1998. At that time, the AAA was 5.9 cm in largest diameter (Fig 1). Chemotherapy with gemcitabine (1 g/m^2 weekly for 3 weeks every 5 weeks) was initiated. The size of the AAA, the pancreatic mass, and the hepatic lesions was followed closely with CT scans. Initially the chemotherapy was accompanied by a prednisone dose of 10 mg/d. However, prednisone was discontinued after 4 weeks because the patient refused further steroid medication. On September 28, 1998, chemotherapy was suspended

From the Division of Vascular Surgery, Department of Surgery, Montefiore Medical Center and Albert Einstein College of Medicine (Drs Chang, Ohki, and Veith); and the University of Cologne (Drs Palm and Russwurm).

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Reprint requests: Frank J. Veith, MD, Montefiore Medical Center, Division of Vascular Surgery, 111 East 210th Street, Bronx, NY 10467.

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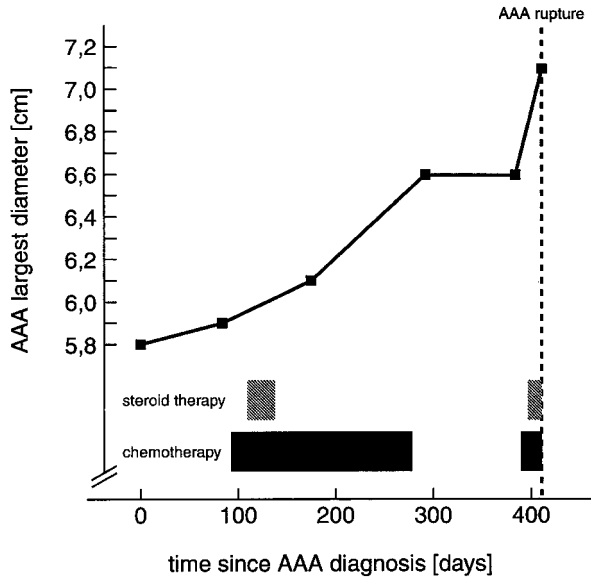

Fig 1. Time course of aneurysm expansion, chemotherapy, and steroid therapy.

according to the patient's wishes. Up to this time, the AAA had grown to 6.6 cm in largest diameter (Fig 1). Chemotherapy was restarted in January 1999 (gemcitabine as previously dosed with cisplatinum added at 30 mg/m^2). Additional medication included dexamethasone at a dose of 10 mg/d (later 12 mg/d), started January 1999. In February 1999, AAA rupture was clinically suspected and confirmed by a subsequent CT scan. At this time the size of the AAA had increased to 7.1 cm in largest diameter (Fig 2, *B, C*). Although an emergency AAA repair was successfully performed on February 8, 1999, the patient died of his pancreatic cancer on March 21, 1999.

DISCUSSION

The current concept of AAA pathogenesis has recently been reviewed in detail.[11-15] Key roles in AAA pathogenesis have been attributed to the decreased elastin concentration and smooth muscle cell (SMC) number; increased collagen concentration and elastolytic activity, mainly matrix metalloproteinases; and an underlying inflammatory response. In this case we have noted unusually rapid aneurysm expansion of 1.3 cm within little more than a year (0.7 cm within the first phase of chemotherapy, equivalent to a growth rate of 1.2 cm/y, Fig 1). Published expansion rates for AAAs of this size range from 0.29 ± 0.9 cm/y to 0.94 cm/y.[16,17] Limet et al[2] reported a growth rate of 0.75 ± 0.13 cm/y in AAAs larger than 5 cm in maximum diameter and showed that aneurysm size itself influences the growth rate in an exponential manner.[2,18] In our patient we observed a 3-month stagnation in aneurysm growth after expansion in size over 10 months. This stagnation coincided with the pause in chemotherapy (Fig 1).

Initially our patient received daily doses of prednisone. Lindholt et al[1] attribute the high prevalence of AAA in patients with COPD to medications commonly used in COPD (such as steroids) rather than to a common pathogenic pathway. They found the mean AAA annual expansion in patients who used oral steroids to be 1.8-fold higher than in the control group. An increased aneurysm growth rate possibly related to steroid treatment has also been noticed in the immunosuppressed transplant population.[19] However, adverse effects of other immunosuppressive drugs may contribute to aneurysm development, such as cyclosporine-induced hypertension.[19] Smith and Hirst[5] reported two cases of spontaneous thoracic aortic aneurysm rupture associated with chronic steroid therapy for rheumatoid arthritis. A case of aortic dissection in a patient with lupus who had been treated with steroids has been described by Hussain et al.[6] In addition, steroids have been shown to induce aortic rupture in heterozygous female Blotchy mice (in 90% of animals within 2 weeks), as well as in healthy mice (in 20% of animals within 2 weeks).[7] Similar effects have been observed in various other rodents.[8-10] On the other hand, in a rat inflammatory aneurysm model, steroids partially inhibited secondary aneurysm enlargement.[20] However, steroids are thought to inhibit SMC proliferation. This was shown in airway SMCs[21] and fibroblasts.[22] Kahari[23] also reports a suppression of elastin gene expression in fibroblasts. This effect may also hold true for AAA and therefore contribute to the disadvantageous effect on AAA of long-term steroid treatment.[1,5-10]

In our patient, steroid treatment was suspended after 4 weeks. In the following 4 months with chemotherapy but no steroid treatment, the aneurysm expanded 0.5 cm (Fig 1). Steroid treatment with dexamethasone was resumed 2 weeks before rupture. We therefore assume that prednisone therapy in this case was not the major cause of accelerated aneurysm growth. However, during the last 2 weeks, treatment with dexamethasone might have contributed to aneurysm enlargement.

Very little work has been published on the effect of chemotherapy on the extracellular matrix. Golden et al[24] report a case of aortic dissection in a patient receiving chemotherapy for Hodgkin's disease.

Unfortunately, they do not discuss the differential effects of each component of their patient's chemotherapeutic regimen, which also included a glucocorticoid. To our knowledge this is the only case report describing large artery rupture possibly resulting from chemotherapy. Most published work investigates vascular complications other than large artery aneurysm formation or rupture. The broad spectrum of vascular toxicity associated with antineoplastic agents has been reviewed by Doll and Yarbro.[25]

Gemcitabine (Gemzar) (chemical name, 2'-2'-difluorodeoxycytidine), a new nucleoside, is increasingly used in the chemotherapy of pancreatic cancer.[26] After intracellular phosphorylation, gemcitabine inhibits DNA synthesis and also reduces cellular deoxynucleotide concentrations.[27] In pancreatic cancer, gemcitabine was found to alleviate cancer-related symptoms, including pain, decreased performance status, and weight loss, and to lengthen survival time (median survival, 5.65 months as compared with 4.41 months with fluorouracil treatment).[28]

The first clinical studies with the anticancer agent cisplatinum were reported in 1974.[29] After intracellular activation, cytotoxic effects of cisplatinum appear to target DNA directly by the formation of a variety of stable bifunctional adducts.[30] In combination with gemcitabine, synergistic effects have been suggested.[31]

In our case, it is remarkable that the fastest aneurysm growth coincided with chemotherapy administration. Whereas the AAA grew 0.7 cm during the first 7 months of chemotherapy with gemcitabine alone and 0.5 cm during the last month of chemotherapy with gemcitabine and cisplatinum, there was no aneurysm growth when chemotherapy was not given for 3 months (Fig 1). Therefore, it seems reasonable to consider a possible correlation between chemotherapy and aneurysm growth. Chemotherapy might have disadvantageous effects on AAAs. Potential mechanisms may involve inhibition of SMC proliferation and collagen and elastin synthesis.

Unfortunately, chemotherapy in pancreatic cancer still remains a largely palliative approach. However, if in other cancers curative chemotherapy is intended, it may be reasonable to lower the threshold for surgical AAA repair. In view of this novel potential adverse effect, chemotherapy should be used with caution in patients with AAA.

Recommendations on follow-up examination of patients with AAA vary depending on aneurysm size and increment of AAA expansion at the last examination.[16,18] At this point, the possible contribution of chemotherapy to accelerated aneurysm growth cannot be ruled out. Therefore, more frequent monitoring of AAAs in patients with large

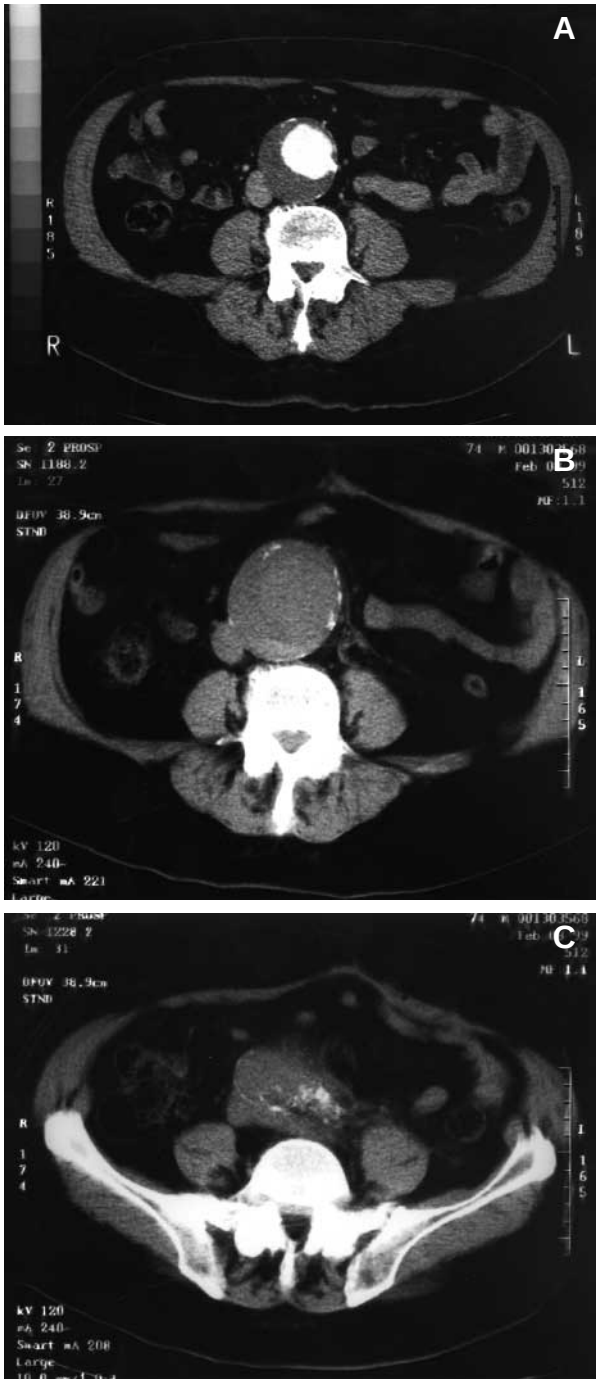

Fig 2. A, CT scan from December 24, 1997 (level L4, AAA 5.8 cm in largest diameter). B, CT scan from February 8, 1999 (level L4, AAA 7.1 cm in largest diameter). C, CT scan from February 8, 1999 (level L5, AAA rupture).

aneurysms is recommended while they are receiving chemotherapy.

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