Thoracic Aortic Aneurysm from Chronic Antiestrogen Therapy

Rishi Tripathi, MBBS¹ Sandeep Sainathan, MD¹ Bulat A. Ziganshin, MD^{1,2} John A. Elefteriades, MD¹

¹Aortic Institute at Yale-New Haven, Yale University School of Medicine, New Haven, Connecticut

²Department of Surgical Diseases, Kazan State Medical University, Kazan, Russia

Address for correspondence John A. Elefteriades, MD, Aortic Institute at Yale-New Haven, Yale University School of Medicine, 789 Howard Avenue, Clinic Building CD317, New Haven, CT 06520 (e-mail: john.elefteriades@yale.edu).

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Abstract

Keywords

- aortic aneurysm
- estrogen
- breast carcinoma

Aortic aneurysms are a common but often undetected pathology prevalent in the population. They are often detected as incidental findings on imaging studies performed for unrelated pathologies. Estrogens have been shown to exert a protective influence on aortic tissue. Pharmacological agents blocking the actions of estrogens may thus be implicated in causing aortic pathologies. We present the case of an elderly woman with breast carcinoma treated for 18 years with antiestrogen therapy who subsequently developed acute thoracic aortic deterioration (enlargement and wall disruption).

The etiological factors causing aneurysm vary with the specific thoracic aortic segment involved.¹ While ascending thoracic aneurysms are commonly caused by inherited connective tissue disorders, such as Marfan syndrome, acquired atherosclerosis-related degenerative atherosclerotic disease usually causes descending thoracic aneurysms.¹ This difference in mechanism also explains the presentation of descending thoracic aneurysms at a later age than ascending thoracic aneurysms.^{1,2}

The incidence of aortic aneurysms is lower in women as compared with men. This gender-related vascular protection has been considered reflective of the anti-inflammatory effects of estrogens (see Discussion).

In this case, we report acute descending thoracic aneurysm formation in a patient with breast carcinoma who was treated with anti-estrogen therapy (selective estrogen receptor modulators and aromatase inhibitors). The patient abruptly developed an aortic aneurysm and aortic wall degeneration after a course of antiestrogen therapy that lasted almost 18 years.

Case Presentation

A 75-year-old female patient with a remote 10 pack-year history of smoking, hypertension, and dyslipidemia was

diagnosed initially with stage I estrogen receptor positive adenocarcinoma of the right breast 18 years ago. She underwent a breast conserving lumpectomy with local radiation to the right breast and adjuvant hormonal therapy with tamoxifen (a selective estrogen receptor inhibitor) for 5 years. She was then transitioned to raloxifene (a selective estrogen receptor inhibitor) for the next 13 years. Unfortunately, the patient developed a regional recurrence of her breast carcinoma in the right supraclavicular and cervical lymph nodes in 2010. She received local radiation to the involved lymph nodes and was switched to letrozole (an aromatase inhibitor, another category of an estrogen inhibitory medication). Due to her frailty and advanced age, palliative chemotherapy was not considered. The recurrence in the cervical region was stable until 2015, when the patient developed widespread bony metastasis. She was admitted to the hospital with shortness of breath. The computed tomography (CT) scan performed as a part of her breast carcinoma metastatic work-up, showed pleural effusions, but also revealed a rapid increase in the size of her descending thoracic aorta from entirely normal 2.8 to 4.7 cm in a short period of 36 days. Her ascending aorta and proximal arch were nonaneurysmal. There was no conventional aortic dissection, but rather the aortic wall in the descending portion appeared to have

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deteriorated and degenerated acutely, with diffuse enlargement and multiple localized flaps giving the distinct impression that the aortic wall was “falling apart” (see ►Fig. 1). The patient was deemed a nonsurgical candidate for this aneurysm because of her advanced stage breast carcinoma. She died several days after hospital admission.

Discussion

Aneurysmal aortic dilation in the descending thoracic aorta relates to degenerative atherosclerotic risk factors, with a genetic disposition as well.¹ This patient had some conventional risk factors for atherosclerosis, such as advanced age,

Fig. 1 Panels on the left (A–D) show a normal aortic arch and thoracic and abdominal descending aorta. Panels on the right (E–H) represent a scan 36 days later: the descending aorta has increased to 4.7 cm and shows localized wall deterioration, with multiple areas of local (not continuous) flap-like appearance (yellow arrow) suggesting that the aortic wall is “falling apart.”

smoking, hypertension, and dyslipidemia. There was no family history of aortic disease.

However, descending atherosclerotic aneurysms usually produce a gradual increase in the aortic size, at an average annual growth rate of 0.10 cm/year.^{1,2} Sudden growth above the expected rates can occur when there is a dissection in the aneurysm. Our patient, however, manifested an alarmingly rapid growth of approximately 2 cm in just 1 month's time, without any traditional associated aortic dissection. The images suggested that the aortic wall was "falling apart." Arteriosclerosis by itself would be an unlikely sole factor in causing this aggressive aneurysmal aortic wall deterioration. There are several other etiological factors, which independently or in addition to degenerative atherosclerosis, could have contributed.

First, there is a possibility of radiation therapy causing arteritis leading to aneurysmal deterioration. This would appear unlikely because the zone irradiated, namely, the right breast and right cervical area, are physically remote from the descending thoracic aorta. The aortic wall may usually become stiff and rigid after radiation, not aneurysmal.³ However, the ascending aorta was normal in this patient, and it is precisely the ascending aorta which should have been the thoracic aortic segment most affected, due to its proximity to the radiation field.

Second, direct metastasis of breast cancer into the thoracic aortic wall has been described.⁴ This, however, would be expected to present as a discrete, possibly positron emission tomography positive mass, rather than a diffuse aneurysmal deterioration of the aorta.

Third, there is a possibility that chronic estrogen suppression contributed to the deterioration of the aortic wall in this case. Although there are, to our knowledge, no clinical case reports of chronic estrogen suppression causing acute or chronic aortic aneurysm, one can postulate a biological basis for estrogen suppression as an etiological factor. Several studies in mice have shown that estrogens, by selectively modulating transforming growth factor- β and angiotensin II-mediated inflammatory pathways in smooth muscle cells in the aortic wall, can retard the aortic aneurysm formation.⁵ This was nicely demonstrated in a mouse model by Johnston et al.⁶ Female mice, which lost a source of estrogen either centrally by an oophorectomy or peripherally by genetically deleting the aromatase enzyme, thus preventing the peripheral generation of estrogen, were more likely to develop aortic aneurysm than the female mice with intact estrogen production. It is precisely on the aromatase enzyme that the drug letrozole (received by our patient) works. Letrozole was this patient's most recent antiestrogen agent. Though this model was based on the abdominal aorta, it is well known that the descending thoracic aorta and the abdominal aorta have similarities in their disease process.¹ Our patient's hormonal milieu was modified similarly to the animal model described above, initially by use of tamoxifen and raloxifene, which are antagonists of estrogen receptors, and later through the use of the aromatase inhibitor letrozole. Letrozole impedes the peripheral production of estrogen in the postmeno-

pausal state. We speculate that letrozole maintained the deprivation of estrogen stimulation in the smooth muscle of this patient's aortic wall, leading to an aneurysm formation.

We found substantial additional experimental and clinical evidence demonstrating the protective effect of estrogens against aneurysm development and growth.⁷⁻¹⁵ This evidence is supportive of the thesis of this report—that antiestrogen therapy may have contributed to a sudden, rapid destruction of the aortic wall in this patient.

With better survival of breast cancer patients and ever-increasing use of antiestrogens, either as adjuvant therapy or as chronic suppressive therapy to retard disease progression in patients with recurrence, the prevalence of thoracic aortic aneurysm in these patients may increase.

Conclusion

We speculate that the antiestrogen agent letrozole may have led to the abrupt deterioration of this patient's descending aorta. Patients with long-term antiestrogen therapy may be susceptible to thoracic aortic aneurysm, which may behave aggressively. This case suggests that on screening CT scans done for tumor monitoring, the descending aorta should be examined carefully for signs of arterial deterioration.

Conflict of Interest

The authors have no conflict of interest relevant to this case report.

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