

Case report

Spontaneous regression of a pulmonary arteriovenous malformation during endocrine therapy for breast cancer

Kohei Hamamoto^{a,*}, Kazushige Futsuhara^b, Emiko Chiba^a, Katsuhiko Matsuura^a, Maya Oishi^a, Noriko Oyama-Manabe^a^a Department of Radiology, Saitama Medical Center, Jichi Medical University, 1-847 Amanuma-cho, Omiya-ku, Saitama, 330-8503, Japan^b Department of Surgery, Saitama Medical Center, Jichi Medical University, 1-847 Amanuma-cho, Omiya-ku, Saitama, 330-8503, Japan

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ABSTRACT

A 52-year-old woman with right-sided breast cancer was diagnosed with a left pulmonary arteriovenous malformation (PAVM) by computed tomography (CT). Percutaneous embolization of the PAVM after treatment of the breast cancer was scheduled to prevent a paradoxical embolic event. She underwent lumpectomy, followed by systemic chemotherapy in combination with tangential field radiotherapy. Subsequently, she received endocrine therapy with tamoxifen, anastrozole, and exemestane, sequentially. There was no change in the PAVM on CT performed during the administration of anastrozole. Subsequently, CT performed five months after switching to exemestane showed obviously decreased size of the affected vessels, and the sac had almost disappeared. To the best of our knowledge, this is the first case report to describe the spontaneous regression of a PAVM during endocrine therapy for breast cancer.

1. Introduction

A pulmonary arteriovenous malformation (PAVM) is a rare clinical condition that involves anomalous direct communication between the pulmonary arterial and venous circulations through a thin-walled sac. A PAVM is strongly associated with hereditary hemorrhagic telangiectasia (HHT) and is present in up to 70% of HHT patients [1]. PAVMs typically remain unchanged in size or enlarge gradually in some cases [1,2]. However, spontaneous regression of a PAVM without any treatment is extremely rare [3,4]. A case of a PAVM that regressed during endocrine therapy with exemestane for breast cancer is reported.

2. Case presentation

A 52-year-old woman was diagnosed with right-sided breast cancer at a local clinic and referred to our hospital for further treatment. Her oxygen saturation (SaO₂) level was 98% on room air. She had no history of dyspnea and no family history of hereditary hemorrhagic telangiectasia (HHT). Blood tests including coagulation tests were within normal limits. A surveillance unenhanced CT scan showed no evidence of metastasis. Additionally, there were abnormal dilated vessels in the left lower lobe (segment 10) of the left lung (Fig. 1). By tracking the

continuity of the blood vessels, a single feeding artery (3 mm in diameter) was seen to arise from the pulmonary artery and was directly connected to a single draining vein (4mm in diameter) via a sac (7mm in diameter). Based on these findings, the patient was diagnosed as having stage I breast cancer with a pulmonary arteriovenous malformation (PAVM) classified as the simple type. Treatment priority was discussed with a surgeon, and the patient chose to have the breast cancer treated first. She underwent breast-conserving surgery, and the pathological diagnosis was stage II invasive breast cancer, estrogen-receptor-positive, progesterone-receptor-positive, and HER2-positive. Postoperatively, the patient received adjuvant chemotherapy with adriamycin, cyclophosphamide, paclitaxel, and trastuzumab in combination with tangential radiation (Fig. 2). Subsequently, she received endocrine therapy with tamoxifen (20 mg), a selective estrogen receptor modulator. However, the drug was changed to anastrozole (1 mg), an aromatase inhibitor, 3 months later because continuous nausea occurred as an adverse effect of tamoxifen. CT performed 1 month after switching to anastrozole showed no change of the PAVM. Three months after starting anastrozole, the drug was changed to exemestane (25 mg), another type of aromatase inhibitor, because the patient had asymptomatic mild elevation of liver enzymes, which was considered to be an adverse effect of anastrozole. At that time, treatment of the PAVM was discussed with the surgeon, and

* Corresponding author.

E-mail address: hkouhei917@gmail.com (K. Hamamoto).

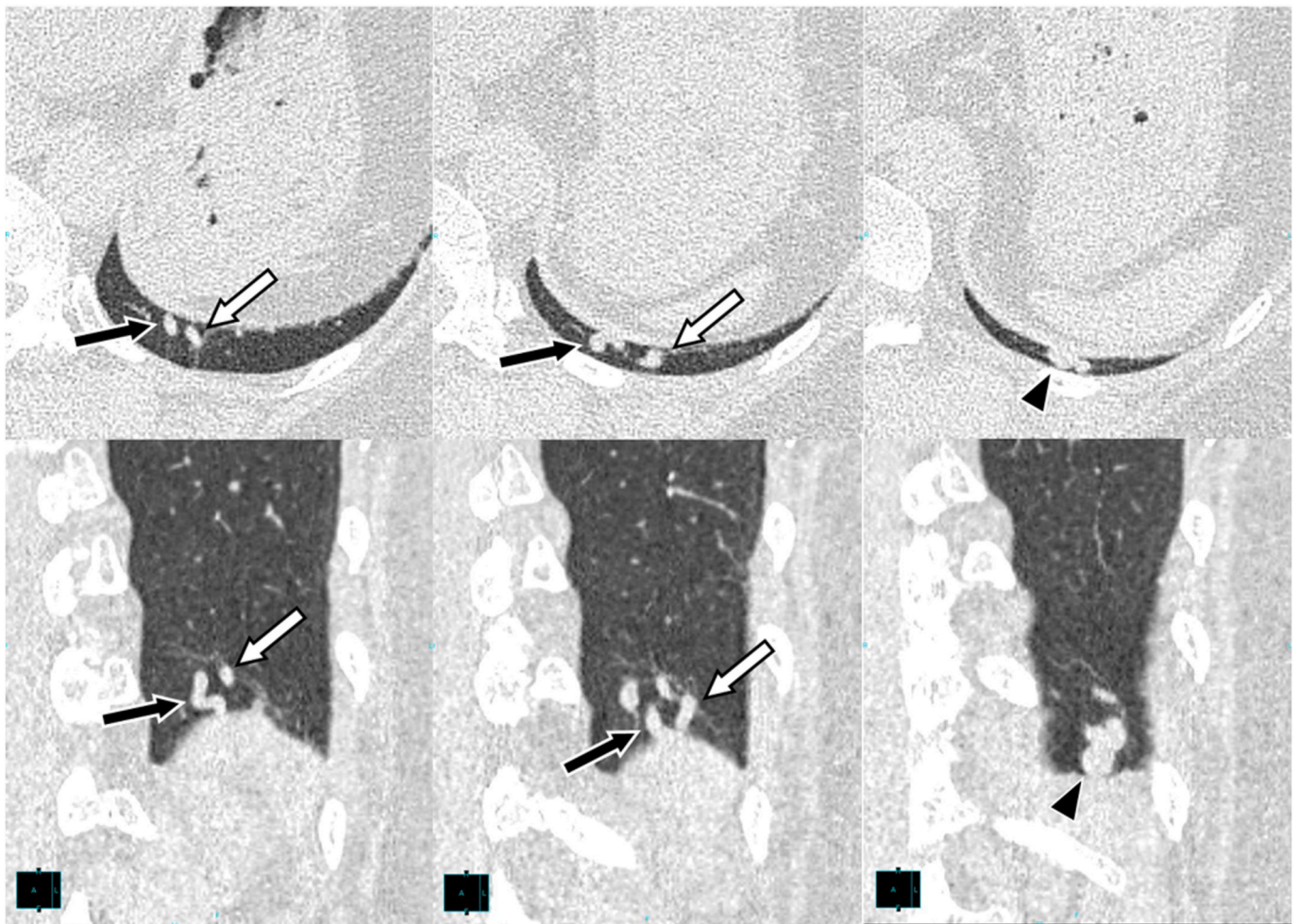


Fig. 1. Computed tomography images of the left lower lobe performed 1 month after starting anastrozole. Upper and lower columns show serial images of axial and coronal views, respectively. Continuity between a feeding artery (white arrow) and a draining vein (black arrow) via the sac (arrowhead).

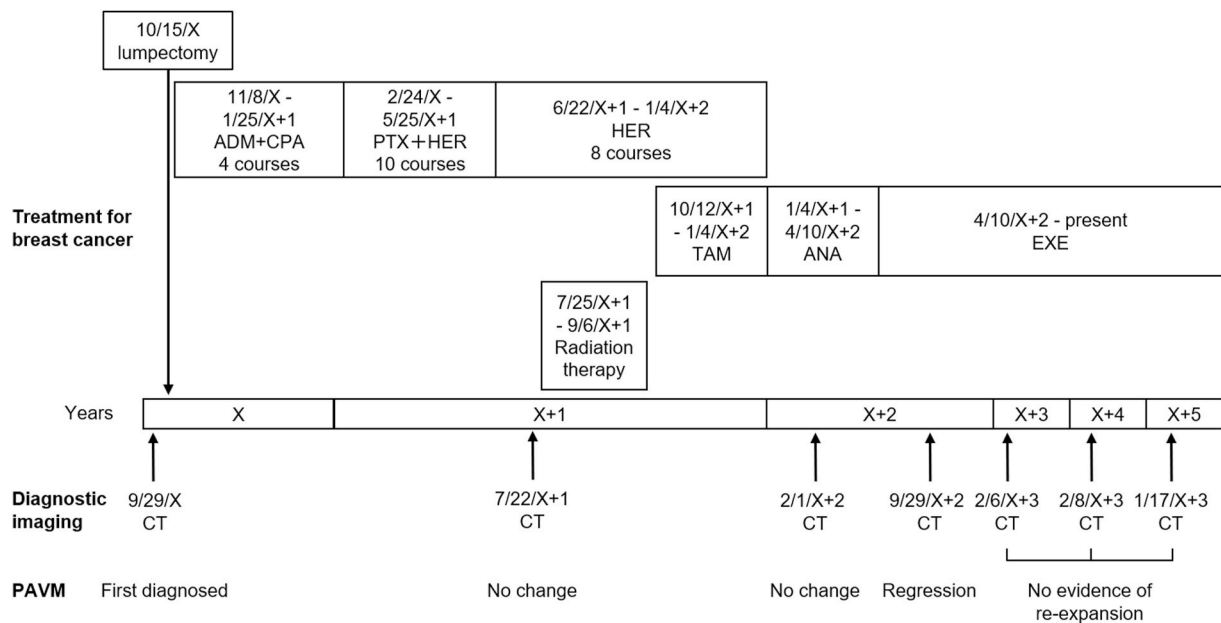


Fig. 2. Summary of the clinical course. ADM: adriamycin, CPA: cyclophosphamide, PTX: paclitaxel, TAM: tamoxifen, ANA: anastrozole, EXE: exemestane.

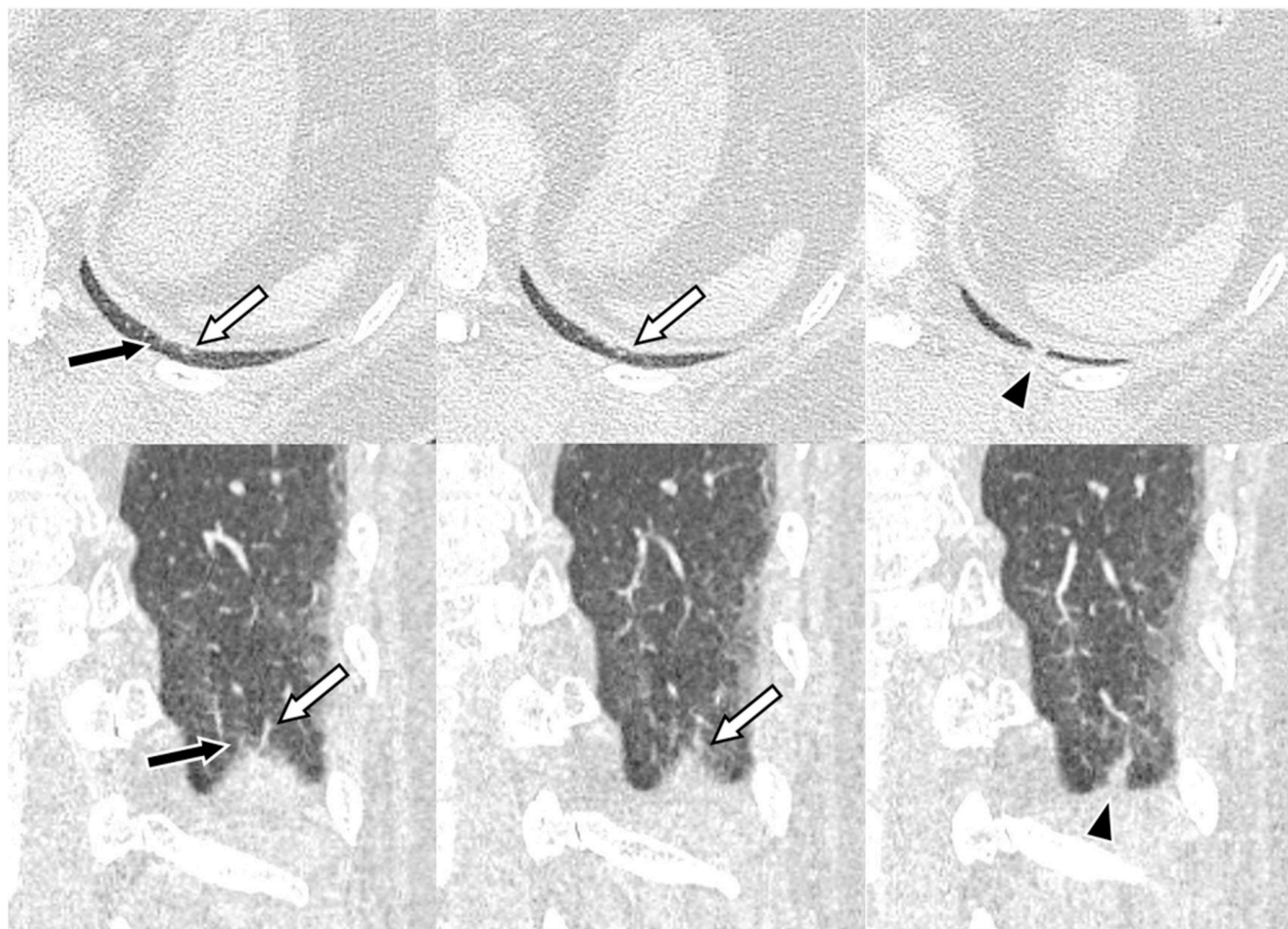


Fig. 3. Computed tomography images performed 5 months after starting exemestane. Upper and lower columns show serial images of axial and coronal views, respectively. The affected pulmonary artery (white arrow) and pulmonary vein (black arrow) are markedly decreased in size, which appear almost equal to those of normal vessels. The sac is also obviously shrunk and appears scar-like (arrowhead).

the patient was scheduled to undergo percutaneous embolization to prevent a potential recurrent paradoxical embolic event with her informed consent. Contrast-enhanced CT was performed 5 months after starting exemestane for preoperative evaluation of embolotherapy, which showed that the affected vessels of the PAVM had obviously decreased in size, and the fistula had almost disappeared (Fig. 3). Additionally, no enhancement of the PAVM was observed. Therefore, treatment for the PAVM was discontinued with the informed consent of the patient. The patient has still continued to take exemestane without any adverse effects. During endocrine therapy, there was no elevation of D-dimer and fibrinogen degradation products (FDP) levels and no obvious changes in blood tests, except a transient elevation of liver enzyme levels. Unenhanced CT performed approximately 3 years after starting exemestane showed no evidence of re-enlargement of the PAVM. Moreover, she did not have any clinical symptoms associated with the PAVM, including paradoxical embolization, brain abscess, hypoxia, or hemoptysis.

3. Discussion

There have been several reports of PAVMs, but the natural history of untreated PAVM has remained unclear. Several clinical studies with serial chest radiographs demonstrated that the majority of untreated PAVMs increase or are unchanged during follow-up [1,2]. The occurrence of PAVM regression without any treatment is extremely rare.

Following a literature search using PubMed, only two reported cases were identified [3,4]. An observational study with serial chest radiographs reported by Vase et al. reported that only one case of 16 untreated PAVMs showed almost complete regression (10-mm decrease in size) over the course of 14 years [3]. Gobara et al. reported a case of PAVM that regressed after acute interstitial nephritis, which required steroid therapy, that was confirmed by CT [4]. To the best of our knowledge, this is the first case with spontaneous regression of a PAVM during administration of an aromatase inhibitor.

The mechanism underlying PAVM regression in the present case is unclear, but there is strong speculation about the hormonal effect of exemestane on the affected vessel, which is based on the following facts: CT performed during systemic chemotherapy, radiation therapy, and administration of tamoxifen and anastrozole showed no change of the PAVM, the patient received no additional medication, and no significant abnormality on blood tests except for mild liver enzyme elevation was seen until PAVM regression was detected. Although the relationship between sex hormones and AVM expansion is well documented, particularly in pregnancy [5,6], reports describing the interaction between a selective estrogen receptor modulator or aromatase inhibitor and arteriovenous malformation have been limited. Rapacciuolo et al. reported a case of hereditary hemorrhagic telangiectasia (HHT) with exacerbation of hypoxemia due to PAVM during endocrine therapy with tamoxifen for breast cancer [7]. Battista et al. described a case of HHT with increasing size of a hepatic AVM that mimicked liver metastasis

during administration of anastrozole as adjuvant therapy for breast cancer [8]. Moreover, an observational study reported by Banc et al. suggested an interaction between the occurrence of a cranial dural arteriovenous fistulas and tamoxifen treatment [9]. These reports are discrepant with the course of the present case, but it is postulated that this discrepancy may be due to differences in drug or patient background characteristics (i.e. HHT vs. non-HHT). Exemestane has a steroid structure and irreversible binding to the aromatase enzyme, causing permanent inactivation even after the drug is cleared from the circulation, whereas anastrozole is a nonsteroidal drug that competitively inhibits the conversion of androgens to estrogens [10]. Moreover, in contrast to anastrozole, exemestane has androgenic, progestogenic, or estrogenic effects, although it has no effect on basal cortisol and aldosterone levels. Based on the fact that tamoxifen and anastrozole did not affect the size of the PAVM, and the estrogen-suppressing effect of exemestane is less than that of anastrozole [10], the regression of the PAVM in the present case might have been due to an estrogen-independent mechanism, as mentioned above (e.g., androgenic, progestogenic, or estrogenic effects of exemestane). Our hypothesis might be supported by several studies reporting that sex hormone receptors including androgen, estrogen, and progesterone receptors are expressed in vascular malformations at various locations, and that androgen and progesterone receptors are more highly expressed in AVMs than estrogen receptors [11–13]. However, these studies did not include PAVMs, and thus, no conclusion could be reached about the relationship between sex hormones and PAVM regression.

Another possible cause of PAVM regression in the present case may be thrombosis of the PAVM due to exemestane, because venous thrombosis is a known adverse effect of this drug, although the incidence is low (1.2%) [14]. To date, a small number of cases of PAVM with spontaneous thrombosis has been reported [4,15–18]. Based on these reports, the incidence of spontaneous thrombosis of PAVMs is estimated to be 0.4–1.8% [15,16]. On the other hand, nearly complete regression of a PAVM has not been reported, except for one case reported by Gobara et al. that showed PAVM regression after acute interstitial nephritis, which was managed by steroid therapy [4]. In that case, the authors strongly believed that the spontaneous thromboembolism of the PAVM itself due to steroid was the major cause of regression of the PAVM because of the elevation of the D-dimer level during the clinical course. In the present case, there was no evidence of thromboembolism based on elevation of D-dimer and FDP levels during the clinical course, and thus, we believe that the hormonal effects of exemestane rather than thrombosis of the PAVM were the main cause of PAVM regression. In any case, the patient continues on exemestane and needs to be followed for PAVM recurrence.

4. Conclusion

A case of PAVM that regressed spontaneously during endocrine therapy with exemestane for breast cancer was presented. Although the precise etiology in this case remains unknown, hormonal effects of exemestane might have been the main cause of this regression.

Author contributions

Kohei Hamamoto: Conceptualization, Writing - Original Draft. Kazushige Futsuhara: Writing- Reviewing and Editing. Emiko Chiba: Writing- Reviewing and Editing. Katsuhiko Matsuura: Writing- Reviewing and Editing. Maya Oishi: Writing- Reviewing and Editing. Noriko Oyama-Manabe: Supervision.

Declaration of competing interest

All authors have no conflict of interest, financial or otherwise.

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