Organising pneumonia caused by hormone (tamoxifen) therapy after radiotherapy for breast cancer: a case report and review of the literature

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Background: Five-year treatment with tamoxifen (TAM) has been the traditional standard of care for breast cancer. Organising pneumonia (OP) is a rare but significant complication of radiation therapy for breast cancer. The effect of TAM leading to OP has not yet been clearly documented.

Case Description: This report describes the case of a 38-year-old female who developed progressive aggravation of round-like patchy bilateral pulmonary infiltrated with a reverse halo sign but without any clinical symptoms 5 months after TAM therapy, following breast-conserving surgery and radiotherapy (RT) for breast carcinoma. A lung biopsy was performed and revealed a histological pattern of OP. TAM therapy was discontinued, and subsequent gradual radiological improvement was observed. As there was no proof for TAM had caused the incident, TAM was re-administrated. Eight months after reinstitution of TAM, the same patchy migratory bilateral pulmonary infiltrated with reverse halo sign was found on chest CT with the patient claiming no discomforts nor any clinical symptoms. The diagnosis of TAM-related OP was made based on the exclusion of other causes and recurrence with the re-administration of TAM. The multidisciplinary team (MDT) concluded that TAM should be withdrawn and a "wait-and-see" approach was taken after a comprehensive assessment, instead of altering the medication or performing prophylactic mastectomy.

Conclusions: The withdrawal and rechallenge of TAM strongly suggest that it may play a role as a cofactor in the occurrence of OP after RT for breast cancer, and RT may also be a cofactor in the occurrence of OP. It is extremely important to be alerted to the possibility of OP after concurrent or sequential hormonal therapy and RT.

Keywords: Case report; breast cancer; organising pneumonia (OP); tamoxifen (TAM); adverse drug reaction

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Introduction

The current systemic and standard treatment for breast cancer is based on a multimodality approach, including surgery, adjuvant chemotherapy, radiotherapy (RT), adjuvant endocrine therapy, and targeted therapy (1). Five-year treatment with tamoxifen (TAM) plus a selective modulator of estrogen receptor function has been the traditional standard of care.

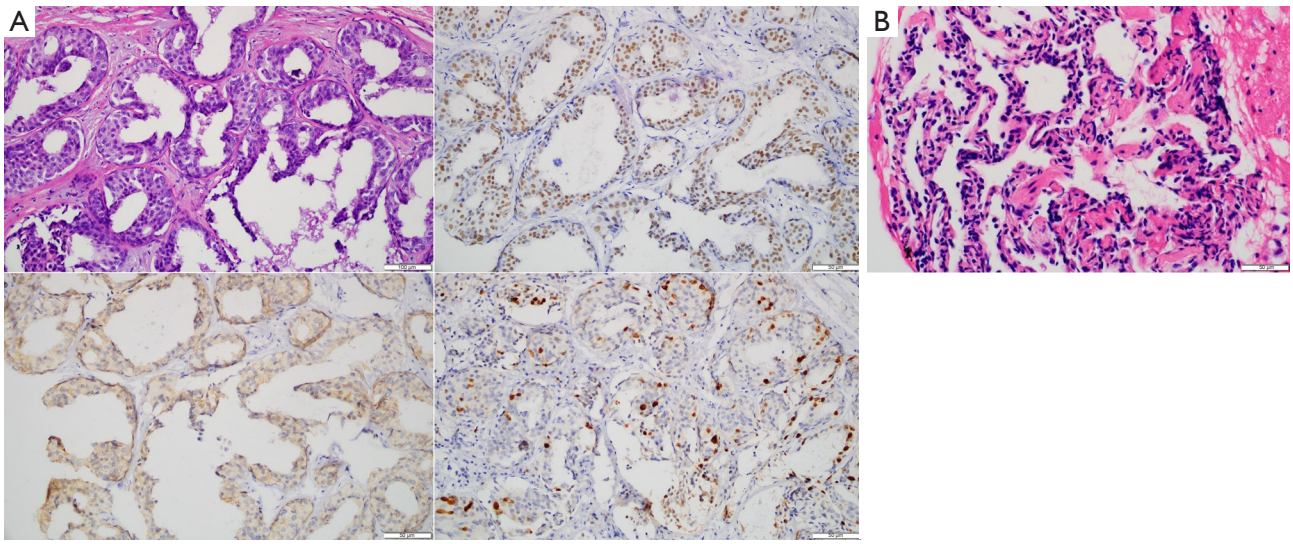

Figure 1 Pathological findings. (A) The pathology of breast revealed intermediate grade ductal carcinoma in situ (T1N0M0). Immunohistochemical staining of the neoplastic cells displayed oestrogen (+60%), progesterone (–) and HER-2 (–) receptors. Hematoxylin and eosin staining (×20) (the top left panel) and immunohistochemistry staining (×20) (the rest panels). (B) The pathology of lung biopsy specimens revealed an interstitial inflammatory infiltrate and fibrous hyperplasia. Focal intra-alveolar fibrin deposition and focal organising pneumonia can be observed within the distal airspaces. Hematoxylin and eosin staining (×40).

Organising pneumonia (OP) (formerly named bronchiolitis obliterans with organizing pneumonia or BOOP) is a rare but significant complication of radiation therapy for breast cancer. Radiation-induced OP reportedly occurs in approximately 2% of patients receiving RT after breast cancer. There are several reported risk factors, including age, central lung distance, and endocrine therapy (2,3). The lung infiltrates often occur outside the radiation port, which is different from radiation pneumonitis. Concurrent or sequential endocrine therapy may promote the development of OP after breast-conserving therapy (4,5).

However, the effect of TAM leading to OP has not yet been documented. So far, only a few cases of OP during the course of trastuzumab therapy have been presented (6-8) but none of them were related to TAM.

This report documents a case of OP related to TAM therapy with the exclusion of other causes. The effect of TAM withdrawal and rechallenge strongly suggests that it plays a role in the occurrence of OP after RT for breast cancer. We present this case in accordance with the CARE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5062/rc).

Highlight box

Key findings

- The withdrawal and rechallenge of TAM strongly suggest that it may play a role as a cofactor in the occurrence of OP after radiotherapy for breast cancer, and radiotherapy may also be a co-factor in the occurrence of OP.

What is known and what is new?

- The development of drug-induced lung injury is a very rare side effect of TAM.
- TAM plays a role as a co-factor in the occurrence of OP after radiotherapy for breast cancer

What is the implication, and what should change now?

- It is extremely important to be alerted to the possibility of OP after concurrent or sequential hormonal therapy and radiotherapy for breast cancer.

Case presentation

A 38-year-old woman was diagnosed with intermediate-grade ductal carcinoma in situ of right breast cancer (T1N0M0) and underwent breast-conserving surgery plus radiation to the chest wall (*Figure 1A*). Previous medical history was unremarkable. The 20 mg TAM once per day was given from approximately 1 month after the initial diagnosis and no other medication was given.

Chest CT performed after 5, 9, and 11 months of TAM therapy revealed an increase of round-like patchy migratory bilateral pulmonary ground-glass opacity with a reverse halo sign. The patient did not declare discomforts nor symptoms. No abnormal laboratory results were recorded. A percutaneous lung puncture biopsy was performed, and the histological pathology revealed an interstitial inflammatory infiltrate and fibrous hyperplasia. Focal intra-alveolar fibrin deposition and focal OP were observed within the distal airspaces (*Figure 1B*).

With the aforesaid observations, the multidisciplinary team (MDT) concluded that the patient was diagnosed with TAM-related OP. Considering the minor clinical symptoms and imaging findings, TAM was withheld after 1-year consumption. Complete resolution was observed three months after TAM withdrawal. As there was no proof for TAM had caused the incident, TAM was re-administrated. Eight months after reinstitution of TAM, the same patchy migratory bilateral pulmonary infiltrated with reverse halo sign was found via chest CT with the patient claiming no discomforts nor any clinical symptoms. MDT with consultants from the breast surgical department, medical oncology, respiratory, and radiology department concluded that TAM should be withdrawn and a "wait-and-see" approach was taken after a comprehensive assessment, instead of altering the medication or performing prophylactic mastectomy. A summary of the timeline is shown in *Figure 2*.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

A case of TAM-related OP was reported on a patient who had undergone breast-conserving surgery and RT for the treatment of breast cancer.

Three points should be discussed for this case: first, the development of OP during the course of TAM therapy and RT; second, the diagnosis and treatment of TAM-associated OP; and the third, the biological mechanisms by which TAM may lead to OP.

Radiation-induced organizing pneumonia (OP) reportedly occurs in approximately 2% of patients who receive RT after breast cancer. There are several reported risk factors, including age, central lung distance, and endocrine therapy (2,3). However, they remain unclear and controversial, and the role of TAM in OP is yet to be fully understood

The process of reaching a clear diagnosis and treatment plan is a key aspect of the case.

Firstly, OP was diagnosed definitely, instead of just a diagnosis of lung injury. A typical feature of OP was shown in the imaging of the case. Most importantly, the histological pathology made a definite diagnosis of OP. Therefore, taking into account of consistent clinical, radiological and pathological features, the diagnosis of OP was concluded.

Secondly, the connection between OP and TAM therapy was established through the withdrawal of TAM therapy, and the recurrence of symptoms with the reinstitution of TAM. In drug-related OP, it is sometimes difficult to determine the causative factor, since it may be associated with various drugs. Therefore, the resolution of OP after stopping the drug, the recurrence of OP with the re-administration of TAM and the exclusion of other causes serves as strong evidence to establish causality. As RT is a well-known cause of OP, it may be a co-factor in the occurrence of OP in this case.

Thirdly, the reasons of the re-administration of TAM and the decision to withdrawal it were concluded by a multidisciplinary team of breast at the Chinese PLA Hospital. (I) After obtaining informed consent, the patient was rechallenged for three reasons: stopping TAM increases the risk of breast cancer recurrence, the lung injury was mild and clinical symptoms were acceptable in this case, and TAM could not be confirmed as the cause of the symptoms. (II) Despite no severe clinical features of OP observed in this case, the decision to withdraw TAM was still made for three reasons: obtaining informed consent, the potential for unforeseeable drug-induced lung damage, and breast carcinoma in situ and no cancer residue in the breast. Therefore, alternative medication or prophylactic mastectomy was not considered. The diagnosis and treatment of this case can serve as a reference for similar cases in the future.

Although Etori *et al.* reported a case of TAM-induced lung injury (9), there are several differences from our case. Firstly, OP was diagnosed definitely in our case, as opposed to just a diagnosis of lung injury. Secondly, the imaging findings of drug-related lung injury are typically bilateral,

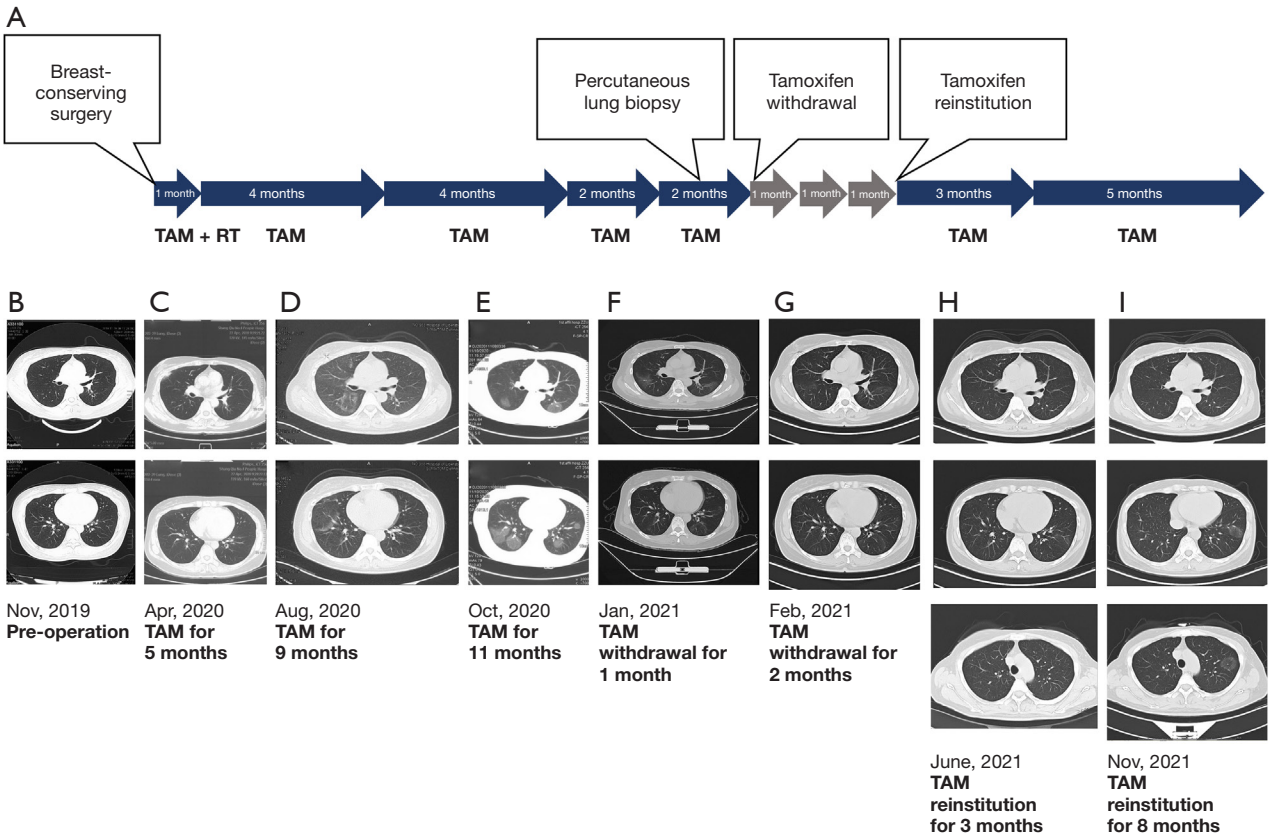

Figure 2 Time line and radiological findings. (A) Treatment timeline. Illustration of the treatment received by the patient. (B) Chest CT performed before operation showed no apparent abnormal findings. (C-E) Chest CT performed after 5, 9, 11 months of TAM therapy revealed an increase of round-like patchy migratory bilateral pulmonary ground-glass opacity with reverse halo sign; laboratory assessment showed no leukocytosis (white blood cell 3.5), no eosinophilia (Eos 0.0), normal inflammatory markers (PCT 0.2, C-reactive protein <3.14), normal Krebs von den Lungen-6 level (KL-6 180), normal thymidine kinase 1 (tk1 0.8) and negative nucleic acid test of COVID-19. Tests for antinuclear antibodies, rheumatic factor, anti-CCP antibody and tumor markers were negative. Serum chemistry and coagulation studies were within normal limits. Blood cultures were negative. Thinprep cytologic test of lung showed some cells with enlarged nuclei and a few lymphocytes. (F,G) Chest CT performed after 1, 2 months stopping the drug showed the improvement of the ground-glass opacity. (H,I) Chest CT performed after 3, 8 months after TAM reinstitution revealed the same round-like patchy migratory bilateral pulmonary ground-glass opacity with reverse halo sign. TAM, tamoxifen; RT, radiotherapy; CT, computed tomography; PCT, procalcitonin; CCP, cyclic citrullinated peptide.

just as in our reported case. However, the case reported by Etori revealed unilateral imaging findings. Thirdly, male breast cancer accounts for less than 1% of all breast cancers and it is treated by extrapolating from treatment for women. The clinicopathological features of male breast cancer, however, differ from those of female breast cancer. Furthermore, biological factors, such as anatomical differences and hormone regulation, may contribute to different responses to treatments. Therefore, the case reported in the literature may not be universally applicable.

Several studies have identified TAM as a risk factor for RT-related lung fibrosis (10,11). As shown by previous studies, TAM in conjunction with RT may increase the incidence of pulmonary fibrosis (PF). The key mechanism is via the induction of TGF-β synthesis. However, the mechanism remains unclarified. Further reports should be accumulated to clarify the characteristic imaging findings and the underlying mechanism of TAM-induced OP.

Conclusions

This report presents that the observation of OP remission

after TAM withdrawal and OP recurrence after TAM rechallenge points clearly towards a role of TAM in OP and RT may be a co-factor in the occurrence of OP.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5062/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5062/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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