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ANCA-POSITIVE PULMONARY GRANULOMATOSIS IN A HER2-POSITIVE BREAST CANCER PATIENT ON ANTI-HER2 THERAPY: CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Introduction: This case highlights the diagnostic complexity of pulmonary granulomatosis in oncology patients, especially when treated with targeted therapy.

Case report: We report the case of a 46-year-old female with metastatic HER2-mutated breast cancer who had received multiple lines of HER2-targeted therapies. The patient presented with suspected lung and mediastinal lymph node progression, despite a good response at other affected sites. A lymph node biopsy revealed non-necrotizing pulmonary granulomas, with negative microbiological testing. Further evaluations showed highly elevated anti-PR3 autoantibodies, while angiotensin-converting enzyme (ACE) and calcium levels remained within the normal range. Pulmonary function tests confirmed a restrictive syndrome. Nasal fibroscopy identified chronic sinusitis with massive nasal polyposis, without renal or cutaneous involvement. High-dose corticosteroid therapy was initiated, leading to a favourable response. Based on the clinical presentation, radiological findings, and pathological features, we concluded that the granulomatosis was related to HER2-targeted therapy.

Conclusion: This case highlights that both an underlying malignancy and specific drugs—such as HER2-targeted therapy—can occasionally contribute to granuloma formation.

KEYWORDS

Sarcoid-like reaction, sarcoidosis, granuloma, HER2, ANCA

LEARNING POINTS

- Differentiating pulmonary granulomatosis is challenging in oncology patients.
- HER2-targeted therapies can induce non-necrotizing lung granulomatosis.

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BACKGROUND

Granulomatous lung diseases are commonly encountered in the daily practice. However, the differential diagnosis is notoriously challenging; in approximately 30% of cases, the diagnosis remains uncertain or unknown[1]. The main aetiology of pulmonary granulomas are infectious causes (55%), with the leading cause being mycobacterial infections, followed by fungal and some parasitic infections[1]. However, the aetiology of non-necrotizing granulomas is most likely non-infectious, with the leading cause being sarcoidosis (around 20% of all patients presenting pulmonary granulomatosis)[1]. Sarcoid-like reactions can also be encountered; they are defined by the presence of non-necrotizing granuloma but without meeting the clinical diagnostic criteria for sarcoidosis. Paraneoplastic and iatrogenic causes for this type of lesion have been identified in genetically predisposed patients. Medications known to cause sarcoid-like reactions are combined antiretroviral therapy, interferon, infliximab and immune checkpoints inhibitors. Other causes of non-infectious granulomatous lung diseases are toxins and exposure etiologies like hypersensitivity pneumonitis, systemic berylliosis, talc pneumopathy, and hot tub lung. Less commonly, immune-related disorders like vasculitis and rheumatoid arthritis can also lead to lung granulomas[1].

CASE DESCRIPTION

A 46-year-old female with a medical history of arterial hypertension and type 2 diabetes was diagnosed in 2017 with locally invasive HER2-mutated breast cancer (pT3N0M0). Initial treatment included mastectomy followed by adjuvant radiotherapy. She relapsed with bone and lymph node metastases 2 years later. The patient received systemic therapy with paclitaxel, trastuzumab and pertuzumab from 2019 to 2021, followed by trastuzumab-emtansine (T-DM1) starting in 2021 after further disease progression.

In August 2023, re-evaluation revealed further disease progression, with lymph node and bone metastases, as well as suspicious pulmonary nodules, likely of metastatic origin *(Fig. 1A and B)*.

A new line of therapy with trastuzumab-deruxtecan (T-Dxd) was initiated. After four cycles, imaging demonstrated a complete metabolic response in bone metastases but worsening hypermetabolic pulmonary and mediastinal lymph node lesions *(Fig. 1C and D)*. Given the suspicion of isolated pulmonary progression, a comprehensive evaluation was performed, including bronchoscopy, bronchoalveolar lavage, and lymph node biopsies. The results showed no neoplastic cells, and microbiological tests were negative. However, lymph node biopsies revealed non-necrotizing epithelioid granulomas *(Fig. 2)*.

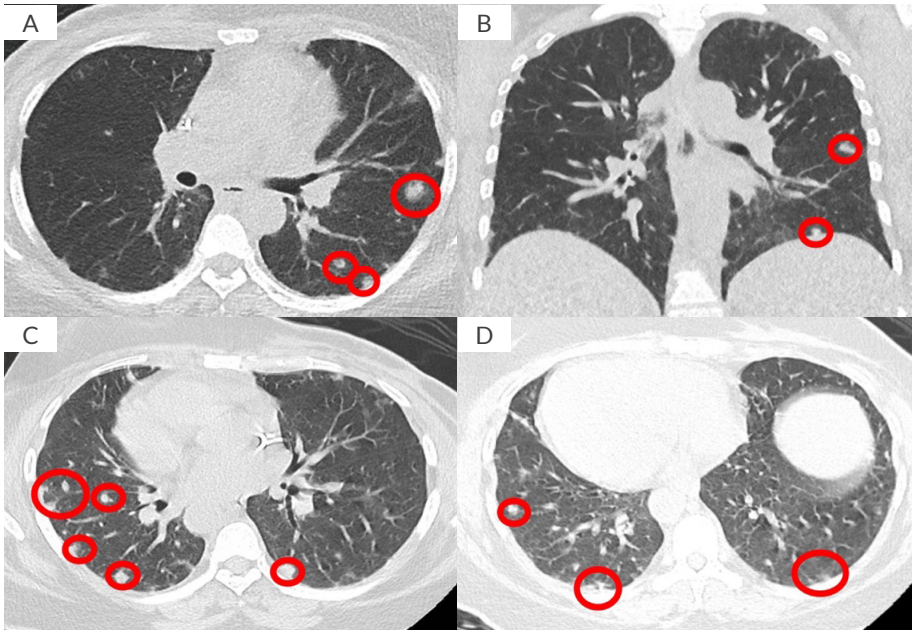


Figure 1. Pulmonary computed tomography-scan: A, B) bilateral and peripheral pulmonary nodules in the upper and lower lobes, (red circles): C, D) Progression of bilateral pulmonary nodes after 4 cycles of T-Dxd, (red circles).

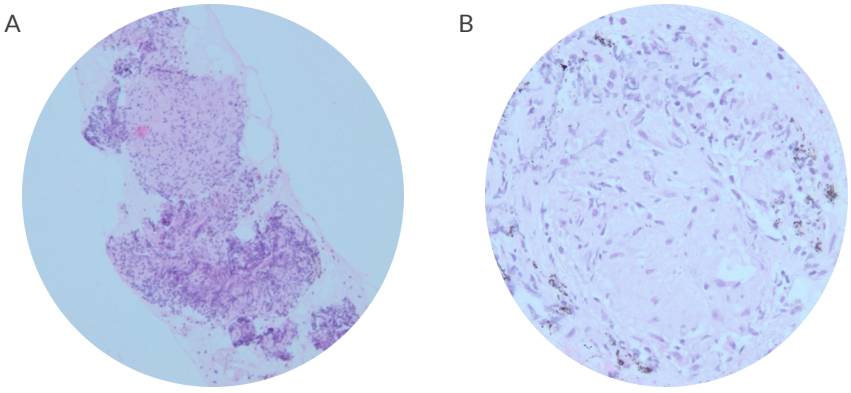


Figure 2. Histopathological examination of the mediastinal lymph node: presence of non-necrotizing granuloma; haematoxylin-eosin coloration, with magnification (A) 10× and (B) 40×.

Classical bacteriological and mycobacterial cultures were negative as well as Ziehl-Neelsen staining on the biopsy. Oncological treatment was suspended. Over time, the pulmonary nodules increased in size and number, and the patient developed respiratory failure along with confusion and disorientation, attributed to a newly identified thalamic metastasis. Immunological studies revealed highly elevated anti-PR3 levels (445.7 U/ml, N < 3.5 U/ml), while ACE and calcium levels remained within the normal range. Pulmonary function tests confirmed a restrictive respiratory pattern. Chronic sinusitis with massive nasal polyposis was identified on nasal fibroscopy. There was no evidence of cutaneous, renal, or neuropathic involvement.

Three main hypotheses were evoked: PR3-positive antineutrophil cytoplasmic antibody (ANCA) associated vasculitis, a cancer associated granulomatosis, and a granulomatosis associated with HER-2 targeted therapies. High-dose corticosteroid therapy with prednisone 1 mg/kg/day was initiated. The patient experienced rapid symptomatic improvement, and a follow-up chest computed tomography scan conducted 3 weeks later demonstrated near-complete resolution of the pulmonary infiltrates *(Fig. 3)*.

The titre of anti-PR3 antibodies also quickly decreased. Corticosteroid tapering was successfully implemented without recurrence of respiratory symptoms.

DISCUSSION

We will explore the different hypotheses to better understand the underlying cause of this pulmonary granulomatosis. It is common practice to exclude an infectious aetiology before discussing the complex differential diagnosis of pulmonary granulomatosis using all the clinical, radiological and pathological patterns[1]. In this case, an infectious cause was highly unlikely as there was no necrotizing granuloma and direct examination, cultures, a polymerase chain reaction test for tuberculosis and Ziehl-Neelsen staining were negative on multiple samples. There were no biological or pathological arguments and nothing in the patient's medical history in favour of a classical toxic or exposure cause. The excellent response to corticosteroid therapy underscored the likely autoimmune origin of this reaction.

Sarcoidosis remained a possible diagnosis, though this would represent an atypical presentation, as macronodules are not characteristic of the disease. Given that sarcoidosis is a great imitator, its diagnosis should be considered cautiously in this context. The clinical and histopathological features were suggestive of ANCA-associated vasculitis (AAV), given the presence of chronic sinusitis with polyposis, pulmonary granulomatous infiltration, and high titres of ANCA autoantibodies, specifically anti-PR3 autoantibodies. AAV can present with pulmonary macronodules; however, the absence of vasculitis or necrosis within the granulomas, along with the lack of renal or cutaneous involvement, argues against this diagnosis. Furthermore, imaging did not reveal any cavitated nodules or pleural thickening, which are commonly observed in AAV. On the other hand, the decrease in ANCA titres following treatment may support an AAV diagnosis, including a drug-induced form, which has been described in association with certain therapies[2].

We then considered a paraneoplastic sarcoid-like reaction (SLR). SLRs have been well-documented in various cancers, including breast cancer, but they typically present as incidental histopathological findings with minimal clinical significance or as pseudo-progressions in already affected tissues[3-5]. This contrasts with our patient, who developed respiratory symptoms, suggesting a more clinically significant manifestation. Cases of paraneoplastic sarcoidosis have also been described, though they are exceedingly rare and usually parallel the course of the underlying malignancy[6]. Given the favourable response of the metastatic disease at other sites, a paraneoplastic cause seemed less likely in this context.

We finally considered whether HER-2 targeted therapies might be implicated. Although pulmonary adverse reactions are uncommon with trastuzumab and other anti-HER2 therapies (such as pertuzumab, T-Dxd, T-DM1), these agents are known to cause interstitial lung disease (ILD) in a small proportion of patients. A meta-analysis of studies conducted on a total of 9.886 patients under HER-2 therapies found an overall incidence of 2.4%, with lower rates observed in patients receiving T-DM1 (0.2-1.1%) and higher ranges in patients receiving T-Dxd (13.6–17.4%) and combinations of anti-HER2 with mTOR inhibitors (7.3–21.4%)[7]. Several risk factors associated with T-Dxd induced-ILD have been reported as certain ethnicities, male patients, age over 60 years, poor performance status, patients who smoke, reduced lung function, history of pre-existing lung disease, but also prior or ongoing treatment with multiple oncologic treatments or thoracic radiotherapy; history of radiation recall pneumonitis and presence of lung cancer or lung

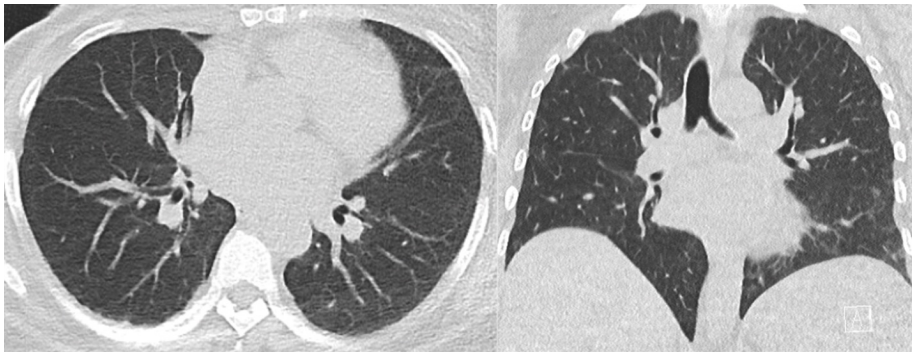


Figure 3. The pulmonary computed tomography-scan reveals resolution of the bilateral nodular infiltration after corticosteroid therapy.

metastases[8]. The radiological presentation of T-Dxd induced-ILD can vary, though cryptogenic organizing pneumonia appears to be the most common pattern (63–72%), followed by acute interstitial pneumonitis (11–15%) and hypersensitivity pneumonitis (3–17%). However, peripheral, well-defined macronodules, as described in our case, have not been described in the literature[9].

In this case, the patient had prior exposure to trastuzumab and T-DM1 before developing grade 2 CTCAE ILD. Whether previous treatment with other anti-HER2 therapies increases the risk of T-Dxd-related ILD remains to be investigated. Nonetheless, several case reports have documented trastuzumab-induced granulomatosis.

First, sarcoid-like reactions have been described in patients taking trastuzumab[5,10]. However, establishing a direct link to the treatment is challenging, as SLR occurs in 4–14% of oncology patients[3]. Sarcoid-like reactions are typically organ limited. They are often asymptomatic and discovered by accident while a progression is suspected on imaging.

In addition, cases of trastuzumab-induced pulmonary sarcoidosis have been described[11-13]. In all those cases, the patient was on trastuzumab, not on other HER-2 targeted therapy like T-Dxd or T-DM1. Symptoms and lung lesions seem to appear after 12 to 40 weeks of treatment. Corticosteroids are not always necessary as the lesions often disappear after trastuzumab is discontinued. However, corticosteroids are sometimes needed in life-threatening cases with complete resolution in most cases. It is important to note that the causality remains uncertain in all those cases as cancer is also considered as a potential trigger for granulomatous reaction. Causality must be suspected based upon a temporal connection between the introduction of the treatment and detection of the disease and upon the evolution after treatment discontinuation.

Finally, 2 cases of trastuzumab-induced ANCA associated lung disease were also reported. Huo et al. reported the case of a 68-year-old male with classical ANCA associated vasculitis affecting lung, kidneys and nasopharynx, after 3 cycles of oxaliplatin, capecitabin and trastuzumab[14]. The exact medication causing the adverse event could not be identified. Chang et al. reported the case of a trastuzumab-induced interstitial lung disease associated with ANCA vasculitis in a 59-year-old woman after 12 cycles of treatment[15]. To our knowledge, this is the first reported case of lung granulomatosis induced by a trastuzumab drug-conjugate.

CONCLUSION

Anti-HER2 therapies appear to be potential triggers of both necrotizing and non-necrotizing granulomas in rare cases. Further studies are needed to determine their exact incidence and the underlying pathophysiological mechanisms. Oncologists should remain vigilant for pseudo-progression or immune-mediated complications in heavily treated cancer patients, as quick diagnosis and appropriate management can significantly impact outcomes.

REFERENCES

1. Nazarullah A, Nilson R, Maselli DJ, Jagirdar J. Incidence and aetiologies of pulmonary granulomatous inflammation: A decade of experience. *Respirology* 2015;**20**:115–121. doi: 10.1111/resp.12410
2. Gao Y, Zhao MH. Review article: Drug-induced anti-neutrophil cytoplasmic antibody-associated vasculitis. *Nephrology* 2009;**14**:33–41. doi: 10.1111/j.1440-1797.2009.01100.x
3. Brincker H. Sarcoid reactions in malignant tumours. *Cancer Treat Rev* 1986;**13**:147-156. doi: 10.1016/0305-7372(86)90002-2
4. Marinos N, Visvikis M, Georgakopoulou VE, Drakopanagiotakis F, Steiropoulos P. Sarcoid-Like Reactions in Breast Cancer Patients: A Report of Two Cases. *Cureus* 2024;**16**:e64096. doi: 10.7759/cureus.64096
5. Sekine C, Kawase K, Yoshida K. Sarcoid-like reaction in a HER2-positive breast cancer patient: A case report. *Int J Surg Case Rep* 2021;**85**:106280. doi: 10.1016/j.ijscr.2021.106280
6. Herron M, Chong SG, Gleeson L, Nicholson S, Fahy RJ. Paraneoplastic sarcoidosis: a review. *QJM* 2020;**113**:17-19. doi: 10.1093/qjmed/hcz207
7. Hackshaw MD, Danysh HE, Singh J, Ritchey ME, Ladner A, Taitt C, et al. Incidence of pneumonitis/interstitial lung disease induced by HER2-targeting therapy for HER2-positive metastatic breast cancer. *Breast Cancer Res Treat* 2020;**183**:23–39. doi: 10.1007/s10549-020-05754-8
8. Henning JW, Brezden-Masley C, Gelmon K, Chia S, Shapera S, McInnis M, et al. Managing the Risk of Lung Toxicity with Trastuzumab Deruxtecan (T-DXd): A Canadian Perspective. *Curr Oncol* 2023;**30**:8019–8038. doi: 10.3390/curroncol30090582
9. Nishino M, Kusumoto M, Bankier AA, Kurihara Y, Zhang L, Rasheed Z, et al. Trastuzumab Deruxtecan-Related Interstitial Lung Disease/Pneumonitis: Computed Tomography Imaging Patterns to Guide Diagnosis and Management. *JCO Precis Oncol* 2023;**7**:e2300391. doi: 10.1200/PO.23.00391
10. Panagiotidis E, Paschali A, Andreadou A, Chatzipavlidou V. HER-2 breast cancer treatment induced mediastinal sarcoid like reaction depicted on 18F-FDG PET/CT. *Hell J Nucl Med* 2021;**24**:159–160. doi: 10.1967/s002449912358
11. Halabi R, Grossman C. Trastuzumab Induced Sarcoidosis Mimicking Metastatic Carcinoma. *CHEST* 2011;**140**:56A.
12. Kogan D, Newton K, Pineda E, Evans A, Guo H, Azumi N, et al. A Case of Trastuzumab-Induced Pulmonary Sarcoidosis. *CHEST* 2012;**142**:1037A.
13. Gupta RK, Mason A, Batra A, Vinayak, Khanduri R, Kumar M. Sarcoidosis associated with Trastuzumab in a young female with carcinoma of breast. *Indian J Tuberc* 2024;**71**:96-98. doi: 10.1016/j.ijtb.2023.06.009
14. Huo B, Lin L, Zhao L, Yu R, Yang J. First reported case of ANCA-associated vasculitis induced by oxaliplatin, capecitabine, and trastuzumab. *Ren Fail* 2023;**45**:2282710. doi: 10.1080/0886022X.2023.2282710
15. Chang CH, Jung CJ, Huang YM, Chiao L, Chang YL, Hsieh SC, et al. The first reported case of trastuzumab induced interstitial lung disease associated with anti-neutrophil cytoplasmic antibody vasculitis - A case report and a prospective cohort study on the usefulness of neutrophil derived biomarkers in monitoring vasculitis disease activity during follow-up. *Breast* 2022;**61**:35–42. doi: 10.1016/j.breast.2021.11.016