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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

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ABSTRACT

Targeted therapies against human epidermal growth factor receptor 2 (HER2) are associated with increased interstitial lung disease (ILD). Trastuzumab, lapatinib, pertuzumab, and trastuzumab emtansine have markedly extended HER2 breast cancer survival but current knowledge on how these HER2-targeted agents induce interstitial lung disease is still poorly defined due to limited cases in the literature. Physicians mostly managed this complication by dose interruption, dose de-escalation, or discontinuation with success. In 2019, the FDA had granted accelerated approval on trastuzumab deruxtecan (T-Dxd) in HER2 breast cancer in the late line setting. Severe ILD incidence rate was over ten percent and led to fatal outcomes in 2.2% of patients in the T-Dxd trial. Searching for biomarkers to detect ILD incidence before it becomes clinically fulminant or for treatment response monitoring is of high clinical value.

A Case of life-threatening trastuzumab-induced ILD was encountered in our facility. The ILD was confirmed to be antineutrophil cytoplasmic antibody (ANCA) pulmonary capillaritis. The biomarker of neutrophil extracellular traps (NETs), serum MPO-DNA complex, showed a good correlation with the clinical severity. Soon after B cell depleting agent rituximab usage, the serum MPO-DNA outperformed ANCA autoantibody and maintained its correlation with clinical severity. In addition to the trastuzumab-induced ILD case, a prospective cohort in our facility also confirmed the usefulness of MPO-DNA in monitoring vasculitis activity. We postulated that upfront testing with biomarkers of vasculitis during HER2 targeted treatment with high ILD incidence may be beneficial in the future.

1. Introduction

The *HER-2* gene is a poor prognostic factor in breast cancer and is amplified in 20–25% of patients [1]. Trastuzumab is a humanized monoclonal antibody that targets the extracellular domain of the human epidermal growth factor receptor 2 (HER2). Since its first approval in 1998, subsequently developed HER2 agents such as

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lapatinib, pertuzumab, and trastuzumab emtansine have markedly extended the HER2 breast cancer patient survival [2–4].

Drug-induced interstitial lung disease (DIILD) accounts for 3–5% of interstitial lung disease. Cancer therapy is the leading cause of DIILD and accounts for 23–51% of the cases [5]. Although the incidence of trastuzumab-related ILD in the registration trials was low at 0.5%, the mortality rate with treatment-related ILD was around 20% [6–8]. In 2019 the novel HER-2 antibody-drug conjugate trastuzumab deruxtecan (T-Dxd) had recently drawn attention for an increased ILD incidence while being approved to treat late-stage HER-2 positive metastatic breast cancer. T-Dxd therapy achieved a response rate up to 60%, but at the cost of ILD up to 13.6%, and 2.2% treatment-related death [9]. Therefore an unmet medical need for developing effective methods in predicting or monitoring HER-2 targeted agents induced ILD is required.

1.1. Case history

A 59-year-old female was diagnosed with invasive ductal carcinoma after undergoing a core needle biopsy for a right breast lump. She received a simple mastectomy, and the surgical pathology showed stage IIA, pT2N0, HER-2/neu 3+, weak positive estrogen receptor (2%), and was negative for progesterone receptor. Adjuvant therapy comprising 12 weeks of weekly paclitaxel plus 52 weeks of tri-weekly trastuzumab was initiated three weeks after the surgery. However, at week 16, the treatment course was interrupted due to an ER visit for blood-tinged sputum over five days.

A chest X-ray showed bilateral centrilobular pulmonary infiltration (Fig. 1A). The complete blood count showed neutrophilic leukocytosis (WBC 11.01 k/μL, neutrophil 74.2%, lymphocyte 17.6%, eosinophil 2.5%), anemia and thrombocytopenia (hemoglobin 9.8 g/dL, platelet 126 k/μL). The coagulation profile, as well as liver and kidney biochemistry, were within normal limits. She was admitted for empirical community-acquired pneumonia treatment with ceftriaxone and azithromycin. However, on the third day, the patient's chest X-ray showed rapid infiltration progression (Fig. 1B), and she had a fever that spiked to 39 °C with hypoxia requiring oxygen mask support. A chest CT with contrast showed diffuse peribronchovascular consolidation (Fig. 1C–D). The culture and serology on multiple pneumonia pathogens, including S. pneumonia, Legionella, Chlamydia, Influenza, *Aspergillus*, Cryptococcus, and CMV virus, showed negative results. Cultures for blood and sputum were also negative. Non-infectious pneumonitis was suspected, and a connective tissue disease survey was conducted. However, hypoxic respiratory failure progressed, and the patient received endotracheal intubation and was transferred to the intensive care unit. The patient underwent a bronchoscopy examination that showed diffuse mucosal bleeding of the entire airway (Fig. 2A and B). Bronchial wash cytology showed neutrophil predominance without malignant cells. Bronchial wash specimens showed no microorganisms, and the cultures remained negative. However, the connective tissue disease survey revealed anti-neutrophil cytoplasmic antibody (ANCA) positivity both via an indirect immunofluorescence method *(IMMCO Diagnostics)* and captured enzyme-linked immunoassays *(EliA)*. The survey showed positive neutrophil cytoplasmic staining (cANCA, cytoplasmic ANCA) and an anti-PR3 titer of 40.28 IU/mL (normal <2.0). The antinuclear antibody, anti-dsDNA, rheumatoid factor, C3, C4, anti-GBM, and anti-SSA/SSB were negative.

A lung biopsy via video-assisted thoracoscopic surgery (VATS) was performed for tissue diagnosis. Microscopically, the resected lung tissue showed marked interstitial fibrosis and residual airspaces of varying size (Fig. 3A). The remaining airspaces revealed extensive hemorrhage, as demonstrated by the presence of erythrocytes and histiocytes mixed with fibrinous exudate in the alveolar spaces. The presence of necrotic neutrophils in the alveolar septa and airspaces were indicative of acute capillaritis (Fig. 3B). A diagnosis of acute capillaritis associated with diffuse alveolar damage of the organizing stage was made (Fig. 3C). Treatment with intravenous methylprednisolone (1 mg/kg/day) was administered. The fever resolved, and the chest X-ray showed improvement on the seventh day. The patient was extubated after 14 days of ventilator support.

Trastuzumab-related ANCA capillaritis was diagnosed after reviewing the patient's history. She had no pulmonary symptoms or chest X-ray abnormality in previous health check-ups. The Naranjo algorithm, an adverse drug reaction (ADE) assessment tool having a scale of 1–10 [10], was applied with trastuzumab scoring 7 out of 10 (Table 1). Probable trastuzumab-related ADE was suspected. Considering this ADE as a life-threatening event, the trastuzumab schedule was permanently discontinued and replaced with hormonal adjuvant therapy. She also received rheumatologist follow up since this event at the outpatient clinic.

1.2. Utilization of different vasculitis markers in the trastuzumab ILD case

Systemic methylprednisolone had induced rapid remission of the chest X-ray infiltration and inflammatory marker (e.g. C-reactive protein, erythrocyte sedimentation rate, D-dimer) improvement during the initial induction period (Table 2). However, the patient still manifested with residual vasculitis disease activity of leg weakness, numbness, and also persistent microscopic hematuria and proteinuria. Occasional expectoration of blood clot content was also noted despite no evident change in the chest X-ray appearance. The measurement of Birmingham Vasculitis Activity Score (BVAS) [11], a tool of vasculitis activity measurement consisted of 9 organs, and a score of 0–33 for persistent symptoms, and 0 to 63 for new or worse symptoms, still scored 10–20 for persistent symptoms in the patient. The patient also encountered a rapid increase in the anti-PR3 titer eight months after discontinuation of trastuzumab (Table 2). Recent evidence has supported neutrophil as the dominant infiltrate within vasculitis lesions [12–14]. And the discovery of neutrophil extracellular traps (NETs), a component of cell-free DNA, histone, proteinase 3 (PR3), and myeloperoxidase (MPO) released by ANCA-stimulated neutrophil, could induce vasculitis damage such as thrombus formation and endothelial damage. The patient was enrolled in a prospective vasculitis cohort in our facility for testing on vasculitis neutrophil-derived NETs and had also started rituximab (500 mg D1/D15, every 6 months) therapy for better control for the DIILD.

2. Prospective cohort on neutrophil derived biomarkers in vasculitis disease activity

2.1. Materials and methods

From 2017 to 2021, a prospective cohort study addressing neutrophil related biomarkers in the evaluation of patients with vasculitis was initiated in our facility (Suppl. Fig. S1). The aim was to explore the relationship between levels of cell-free MPO-DNA, a biomarker for NETosis and the clinical activity of systemic vasculitis. Including the Case presented in the manuscript, a total of eight patients with vasculitis and 17 healthy controls (a ratio of 1:2) were enrolled, and serial serum testing was obtained (Suppl. Fig. S2). The study was approved by the hospital Institutional Review Board in 2017 (NTUH: 201612147RINA). Informed consents were obtained from all patients and healthy donors.

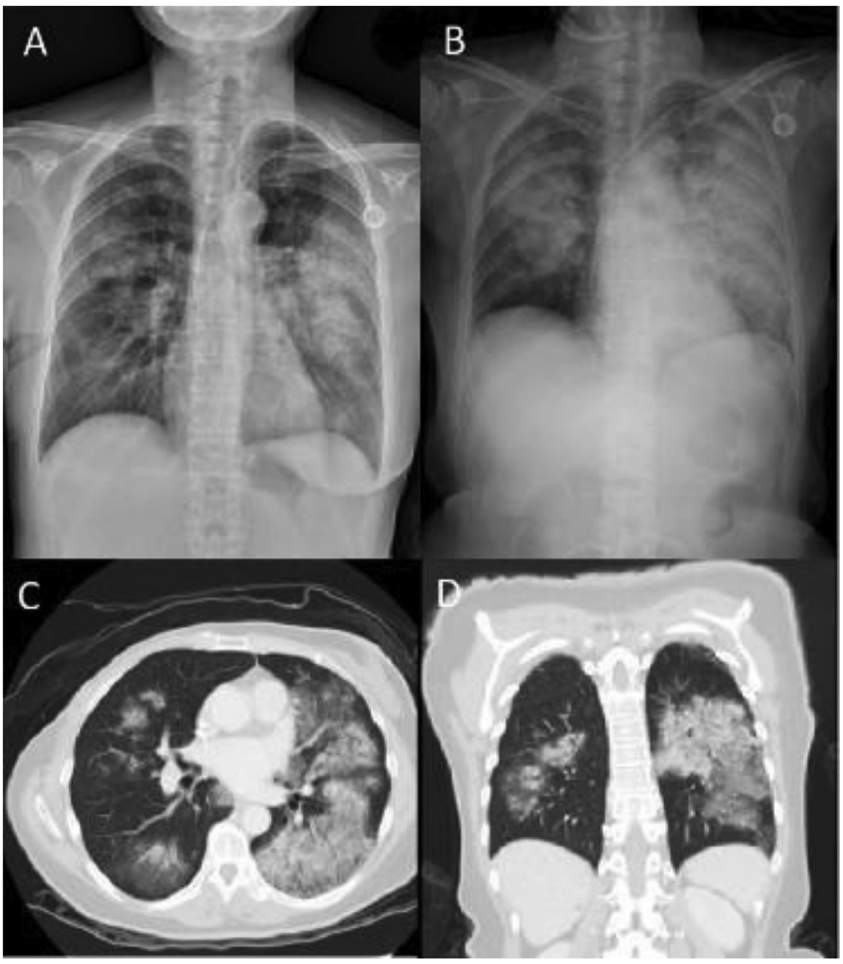


Fig. 1. A-D. (A) Chest radiograph (CXR) at initial presentation revealed multi-lobar consolidation with a centi-hilar pattern. (B) CXR on the third day showed rapid bilateral pulmonary infiltrate progression (C–D) Computed tomography (CT) on the third day showed a diffuse, multi-lobar consolidation with a peri-bronchovascular pattern.

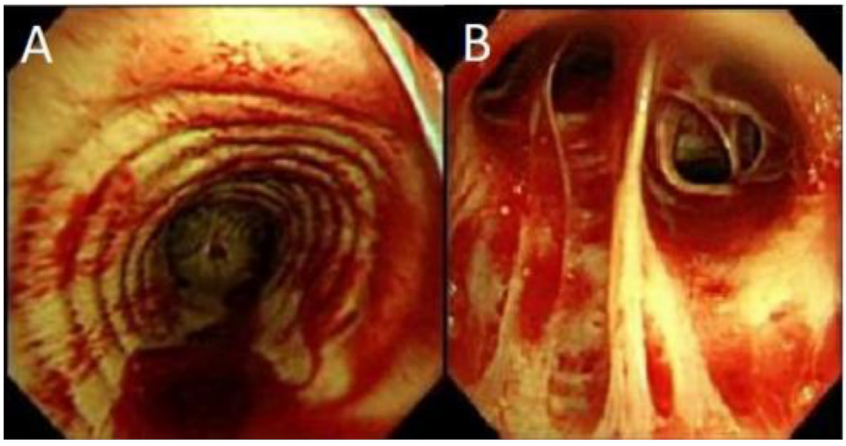


Fig. 2. A-B Bronchoscopy examination of the tracheal (A) and main carina (B) revealed fresh blood in the whole airway without active vascular bleeding.

2.2. Measurement of MPO-DNA and ANCA

We tested each vasculitis individual for the cell-free MPO-DNA via a "sandwich" ELISA with an anti-MPO polyclonal antibody (GeneTex, GTX22088, Irvine, Ca, USA). ELISA microplates were coated with the MPO monoclonal antibody overnight to capture MPO-associated DNAs. Anti-ds DNA-specific monoclonal antibodies (Abcam, Cambridge, ab27156, UK; 1:2000) were added to bind MPO-associated DNA, followed by binding of a horseradish peroxidase-conjugated anti-mouse IgG antibody (Jackson ImmunoResearch, 115-035-003) for detection. A peroxidase substrate (3,3′,5,5′-Tetramethylbenzidine) was added to react with the

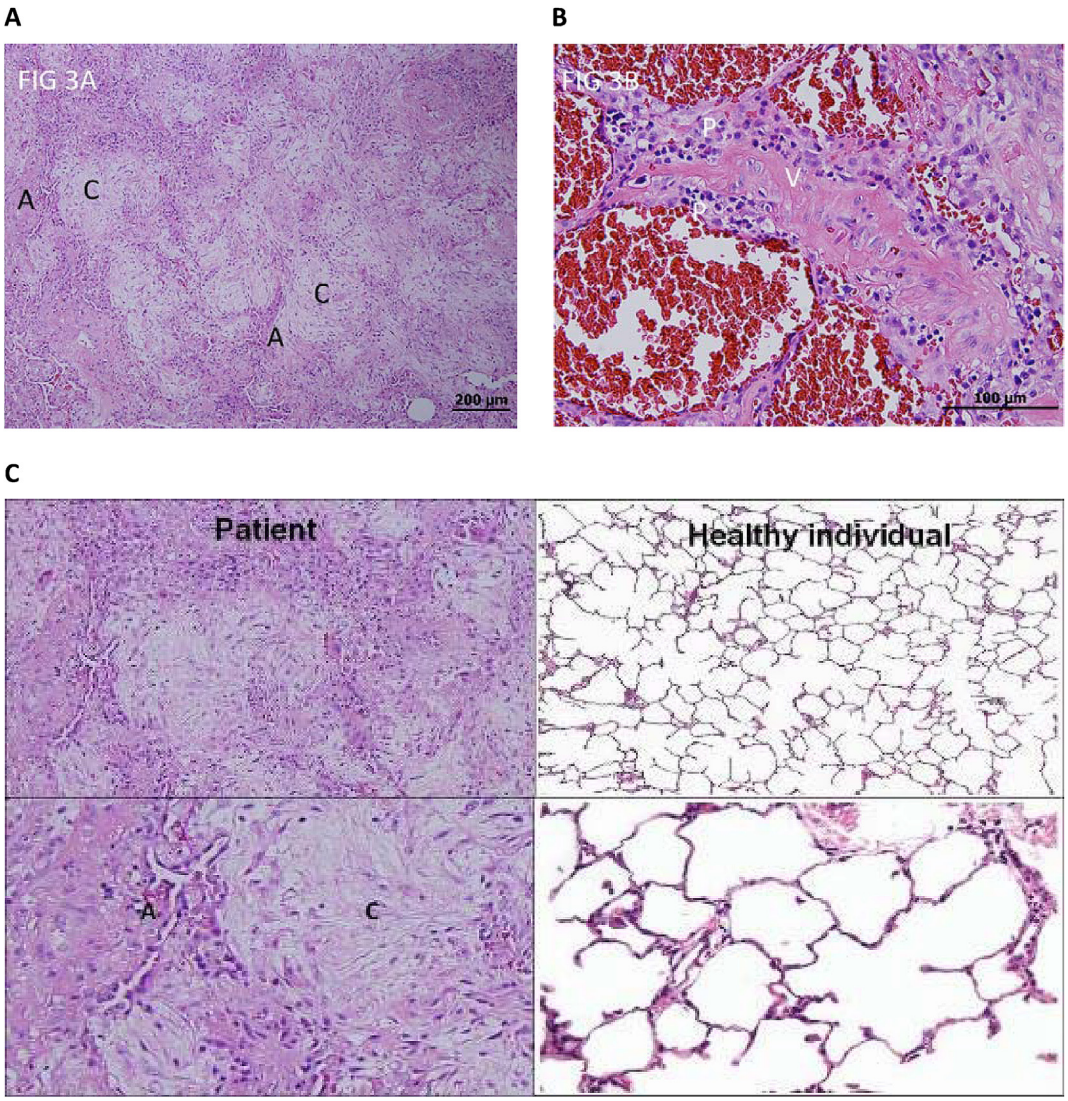


Fig. 3. A Lung, left upper lobe, wedge resection, low power field (100X), interstitial fibrosis with collagen deposits (C) and alveolar airspace obliteration (A). **B** High power field showing alveolar hemorrhage (A), and necrotic neutrophils (P) in a capillary wall (V) and alveoli**. C** Comparison of the patient sample to a sample from a healthy individual shows marked airspace obliteration due to hemorrhage and interstitial thickening.

Table 1
Probable Trastuzumab related adverse drug reaction, with Naranjo score of 7 according to the patients clinical history.

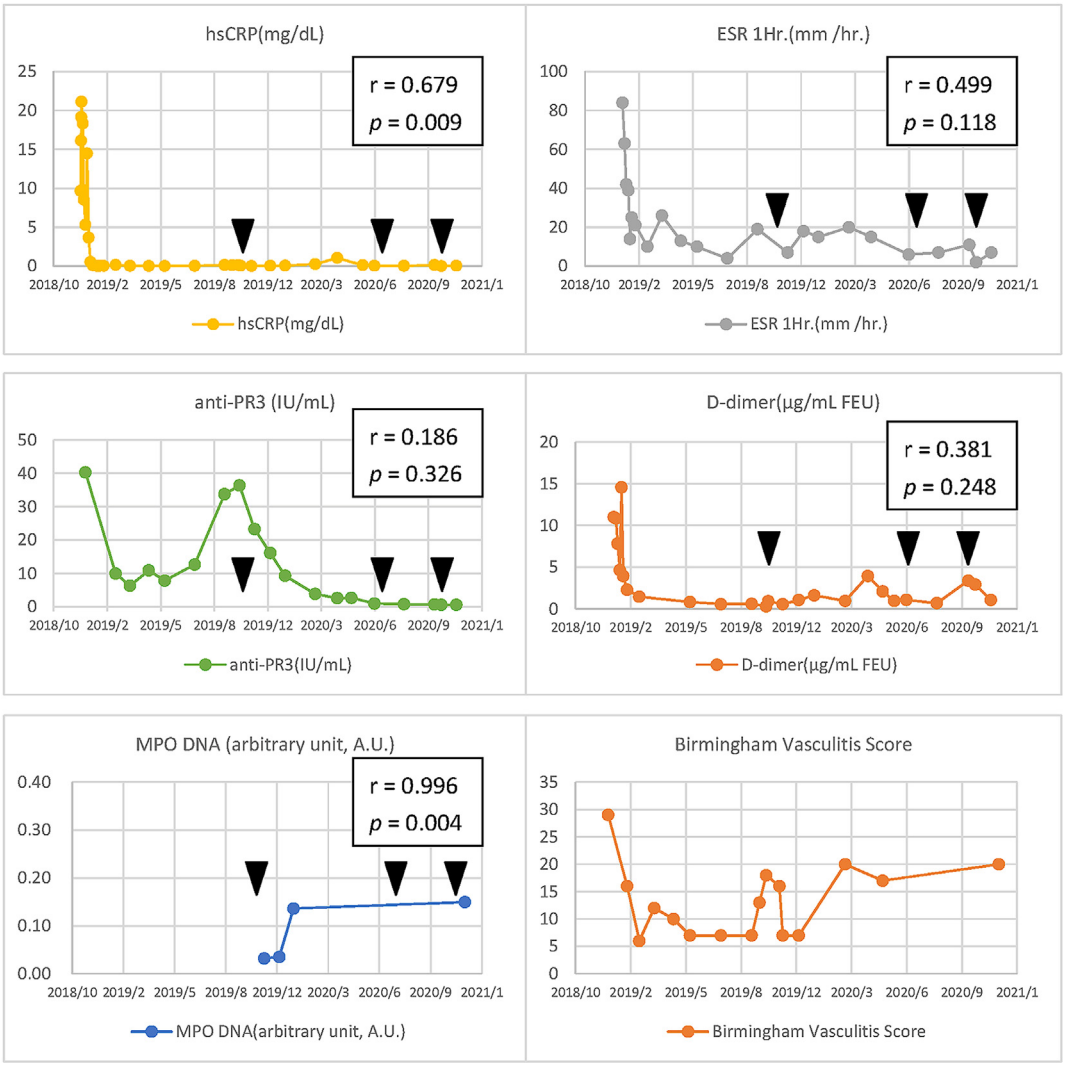
No	Question	Yes	No	Do Not Know
I	Are there previous conclusive reports on this reaction?	+1	0	0
II	Did the adverse event appear after the suspected drug was administered?	+2	−1	0
III	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
VI	Did the adverse reaction reappear when the drug was administered?	+2	−1	0
V	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0
VI	Did the reaction reappear when a placebo was given?	−1	+1	0
VII	Was the drug detected in the blood (or other fluids) in concentration known to be toxic?	+1	0	0
VIII	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
IX	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
X	Was the adverse event confirmed by any objective evidence?	+1	0	0

Naranjo score for estimating the probability of adverse drug reactions; 0, doubtful ADR; 1–4 possible ADR; 5–8, probable ADR; ≥9 definite ADR.

conjugated peroxidase to yield a blue product. The reaction was halted by adding 2 N H_2SO_4, and the absorbance of the final product was measured at 450 nm and was transformed to an arbitrary unit (a.u.) according to the previous study [15]. An MPO-DNA assay standard curve is provided (Suppl. Fig. S3).

ANCA assessment was performed using anti-proteinase (PR3) and anti-myeloperoxidase(MPO) specific immunoassays (EliA; Thermo Fisher Scientific, Waltham, MA, USA). The assay was performed according to the manufacturer's instructions. An antibody concentration was considered positive if: MPO >5.0 IU/mL and PR3

Table 2
Trend of inflammatory markers since interstitial lung disease event onset; arrowheads indicate rituximab treatment. MPO-DNA showed a good correlation with Birmingham Vasculitis Activity Score (BVAS), especially in the late phase ($r = 0.996$, $p = 0.004$) after Rituximab treatment. This AAV patient had a protracted disease course that involved BVAS score rebound despite the PR3 autoantibody titer remaining below the upper limit. The results indicate that the MPO-DNA complex, which is a novel biomarker of neutrophil activation, could better monitor vasculitis activity.



>3.0 IU/mL (normal range were provided by the manufacturer).

2.3. Statistical analysis

We utilized Stata statistical software (V. 14.0, Stata Corporation, College Station, TX) for the analysis. The MPO-DNA cut-off point between healthy controls and vasculitis patients was obtained according to the maximum Youden index (Sensitivity + Specificity - 1) to capture the performance of this dichotomous diagnostic test [16]. Statistical significance of the difference between two sets of continuous variables was analyzed using a Mann-Whitney *U* test. A *p*-value less than 0.05 was defined as statistically significant.

3. Results

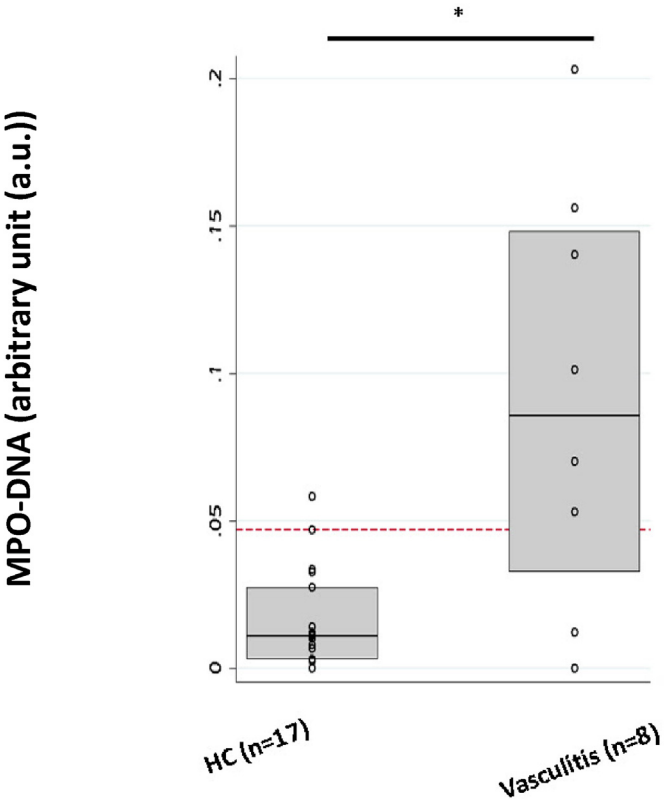
3.1. MPO DNA performance in the prospective vasculitis cohort

The MPO-DNA values were significantly higher in the systemic vasculitis group (n = 8; 0.092 ± 0.071 arbitrary unit (a.u.)) relative to healthy donors (n = 17; 0.015 ± 0.018 a.u., $p = 0.01$) (Table 3). The Youden J index representing the maximum potential effectiveness of the upper-lower limit of the MPO-DNA cut-off value was 0.047 (a.u.), the red dashed line (Table 3). An MPO-DNA cut-off level at ≤ 0.047 a.u. was established to differentiate between healthy control and vasculitis patients. We also tested MPO-DNA serum level, erythrocyte sedimentation rate, C-reactive protein correlation with their Birmingham Vasculitis Activity Score. The MPO-DNA showed a moderate positive correlation [r (n = 12) = 0.596, $p = 0.025$]; but the C-reactive protein [r(n = 10) = 0.402, $p = 0.196$] and the erythrocyte sedimentation rate [r(n = 9) = 0.119, $p = 0.727$] showed no correlation with clinical vasculitis severity. These results suggest that MPO-DNA levels may also be useful in monitoring vasculitis activity compared to standard inflammation biomarkers (Table 4).

3.2. MPO DNA performance in the trastuzumab ILD case

During follow-up of the Case presenting trastuzumab-induced

Table 3
MPO-DNA values were significantly higher in the systemic vasculitis group [n = 8; 0.092 ± 0.071 arbitrary units (A.U.)] relative to healthy donors [n = 17; 0.015 ± 0.018 A U., $p = 0.01$]. Youden J index representing the maximum potential effectiveness of the upper-lower limit of the MPO-DNA cut-off value, which was set at 0.047 (A.U.), as indicated by the red dashed line.



ILD, we found that despite standard vasculitis anti-PR3 is capable of showing good correlation during initial glucocorticoid therapy with the Birmingham vasculitis score (BVAS). The correlation was lost after salvage treatment with the B-cell targeting agent rituximab was initiated (Table 2). MPO-DNA levels exhibited a better correlation with the clinical vasculitis activity BVAS score during the rituximab treatment period.

4. Discussion

Interstitial lung disease (ILD) induced by HER2-targeted agents is a well-known adverse drug reaction, but the mechanism is ill-defined and considered low in incidence [17]. HER-2 targeted agents such as trastuzumab, trastuzumab emtansine had been reported to induce cutaneous vasculitis in the previous literature [18–20], but pulmonary vasculitis due to HER2 targeted agents had not been reported yet.

A recent review of 9886 patients investigating anti-HER2 therapies for HER2 breast cancer had reported the overall incidence of ILD was 2.4%. The incidence of grade 1–2, grade 3–4, and grade 5 events were 66.7%, 23.0%, and 0.2% respectively. The agents leading to the highest ILD incidence was trastuzumab combined with everolimus or paclitaxel. The incidence of ILD-related deaths was highest among patients receiving trastuzumab deruxtecan (T-Dxd), with an incidence of around 2% [17]. Recently the oncology society has drawn attention to this adverse event due to the recent accelerated approval of T-Dxd [9,21]. The novel antibody-drug conjugate had shown a 60% response rate in third or later line metastatic HER-2 positive breast cancer but at the cost of treatment-related ILD up to 13% and 2% treatment-related death. This high rate of side effects will inhibit its potential to be utilized as the frontline therapy or even be placed in the curative adjuvant or neoadjuvant setting.

Table 4
The MPO-DNA serum levels, erythrocyte sedimentation rates, and C-reactive protein correlation with the Birmingham Vasculitis Activity Score for the eight vasculitis patients, the MPO-DNA showed a moderate positive correlation but the C-reactive protein and erythrocyte sedimentation rate did not.

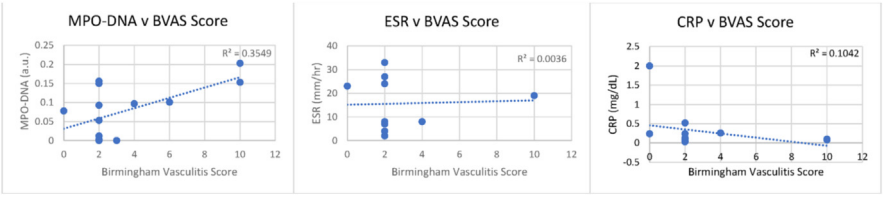


Table 5
Case comparison of previously reported trastuzumab-related interstitial lung disease [12–17].

Case	Age Gender	Previous CRT (setting)	Tmab exposure	CT pattern	Pathology	Treatment	Recovery	Naranjo Score
1	49 F [23]	AC, RT, D (adjuvant)	3 months	Subpleural consolidation	Organizing pneumonia	n/a[a]	Yes	6
2	56 F [25]	FAC, D (salvage)	4 months	Consolidation and pleural effusion	BAL: eosinophil 18%	Prednisolone (40 mg/d)	Yes	8
3	51 F [26]	P (neoadjuvant)	10 weeks	Ground glass opacity	TBLB: Intra-alveolar hemorrhage, interstitial inflammation	Prednisolone (40 mg/d)	Yes	6
4	63 F [24]	D (neoadjuvant)	5 weeks	Peripheral consolidation, GGO	Diffuse alveolar damage	Prednisone[c]	No (mortality)	7
5	67 F [35]	DC (adjuvant)	4 months	GGO	n/a	Prednisone Cyclophosphamide[b]	Yes	8
6	68 F [28]	EC (adjuvant)	3 months	Patch infiltration, GGO	n/a	Semi-pulse steroid[c]	Yes	6
7	62 F [28]	DC (adjuvant)	3 months	Patchy consolidation, poorly defined nodules	n/a	Prednisolone[c]	Yes	7
8	71 F [36]	Salvage Tmab followed by T-DM1	Tmab 12 wks T-DM1 6 wks	Diffuse interstitial infiltrates	n/a	Methylprednisolone (1 mg/kg/d)	Yes	5
9	59 F	P (adjuvant)	3 months	Patchy consolidation	ANCA capillaritis, acute interstitial pneumonia	Prednisolone (40 mg/d)	Yes	7

CRT, chemoradiotherapy; Tmab, trastuzumab; T-DM1, trastuzumab emtansine; GGO, ground glass opacity; A, doxorubicin; C, cyclophosphamide; RT, radiotherapy; F, 5-fluorouracil; P, paclitaxel; D, docetaxel; BAL, bronchoalveolar lavage; TBLB, transbronchial lung biopsy.
[a] Resolved spontaneously after trastuzumab discontinuation.
[b] Cyclophosphamide was used upon trastuzumab rechallenge.
[c] The dose used was not reported.

A recently published article by Kumagai et al. had reported successful induction of T-Dxd interstitial lung disease in a cynomolgus monkey model. Receiving T-Dxd in a monkey model developed interstitial lung disease, whereas receiving Dxd does not. Although most ILD lesions were found within the alveoli, the HER2 expression in lungs was limited to the bronchial level [22]. Vasculitis due to a pathway via ANCA autoantibodies, an indirect mechanism by the immune system, could explain why the injury was not at the location where T-Dxd was uptaken. Moreover, a two-step mechanism of pathogenesis explains how DIILD (drug-induced ILD) manifests later after anti-HER2 therapies. A literature review was performed to summarize previously reported cases of trastuzumab-related ILD. A total of 8 cases were identified before our Case [23–28]. Two of the reported cases had available pathology that showed organizing pneumonia or diffuse alveolar damage. No traceable serum marker was reported in previously reported patients. All previously reported cases that we identified had late onset with a median time of onset two months after the first trastuzumab exposure (Table 5). The pattern of CT infiltration largely comprised ground-glass opacity and patch consolidations, with only one case exhibiting nodular lesions. Most patients recovered following prednisolone-based monotherapy, and only one patient died. Long-term follow up was not conducted in these cases. Our case also had a protracted course of vasculitis up to two years. We found that both ANCA auto-antibody testing and NET related biomarker, MPO-DNA should be tested concomitantly and especially when B cell depleting agents (such as rituximab use in our case) inhibit the autoantibody production, but vasculitis-related neutrophil activity is still high. Reliance on ANCA autoantibodies alone to monitor vasculitis activity may not be sufficient.

Systemic glucocorticoids combined with either rituximab or cyclophosphamide are recommended for induction therapy for life-threatening AAV [29]. Autoreactive B cell depletion by rituximab can effectively reduce disease activity and decrease pathogenic ANCA concentrations in AAV patients. Although adverse events after rituximab include hepatitis B reactivation [30] and progressive multifocal leukoencephalopathy [31], the safety profile of rituximab is still considered to be favorable. Further salvage therapy or investigational agents included belimumab [32], a monoclonal antibody against soluble B cell-activating factor (BAFF) that can induce B cell apoptosis and showed clinical activity as an add-on therapy. The use of therapeutic plasma exchange is also beneficial for carefully selected patients experiencing severe diffuse alveolar hemorrhage or a serum creatinine level of $\geq$500 mmol/L [33].

There are still two crucial pieces of information that cannot be determined from our Case. First, neither serum levels of anti-PR3/anti-MPO level prior to trastuzumab exposure were available for this case. A prospective examination of vasculitis markers may be considered in the future to determine whether ANCA has clinical utility in predicting side effects during HER2 targeted therapy, especially antibody or antibody drug-conjugates. Secondly, the majority of drug-induced AAV cases present with anti-MPO positivity [34], but our case presented with anti-PR3 positivity without any upper airway symptoms or granuloma formation. Whether this difference is related to the medication administered or due to individual patient differences cannot be explained at present.

In conclusion, this Case is the first clinical evidence of HER-2 targeted therapy induces pulmonary ILD via ANCA autoantibodies. Early suspicion with testing of ANCA level can be life-saving when a biopsy cannot be immediately obtained. Pre-treatment ANCA level testing may also be considered in the future when treating patients with HER-2 agents with higher risk profiles of ILD. In addition, serum MPO-DNA, could be a biomarker with promising clinical implication, as the results from this case and a prospective vasculitis cohort in our facility indicated.

Authors' contribution

C.H.C., Y.M.H., and Y.M.K., wrote the original draft writing with input from all authors; Y.M.K., C.J.J., designed, developed and conducted the experiments; Y.M.K., L.C., are the primary physicians responsible for the patient medical treatment; Y.L.C., reviews the surgical pathology and issues the report.; S.C.H., Y.M.H., C.H.L., contributed to the final version of the manuscript; All authors actively participated in the discussion and suggestion for the manuscript.

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Ethics approval

This study was approved by the hospital Institutional Review Board (NTUH: 201612147RINA). The informed consent was obtained from the patients.

Availability of data and material

The author(s) confirm that the data supporting the findings of this study are available within the article.

Code availability

The author(s) confirm that the data supporting the findings of this study are available within the article.

Declaration of competing interest

The author(s) had declared that no conflicts of interest exist.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.11.016.

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