Journal of Neuroimmunology 353 (2021) 577505

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Natalizumab induced blood eosinophilia: A retrospective pharmacovigilance cohort study and review of the literature

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ARTICLE INFO

Keywords:
Natalizumab
Side effects
Pulmonary eosinophilia
Immunotherapy
Multiple sclerosis

ABSTRACT

Objective: To describe frequency of natalizumab related eosinophilia and clinical symptoms of eosinophilic disease in our monocentric cohort.
Methods: Comparison of clinical characteristics of 115 natalizumab treated and 116 untreated RRMS patients and review of literature.
Results: 38% of natalizumab treated patients had eosinophilia, which occurred significantly more frequently compared to untreated MS patients (3%, p-value<0.001). In symptomatic patients, mean eosinophil counts were significantly higher than in asymptomatic patients and symptoms developed within one year.
Discussion: Eosinophilia is a side effect of natalizumab and mostly asymptomatic. However, few patients develop within one year after start of natalizumab an eosinophilic disease as severe side effect.

1. Introduction

Natalizumab (NTZ) is commonly used as treatment in relapsing remitting multiple sclerosis (RRMS). NTZ acts as a selective adhesion molecule antagonist, which binds very late antigen (VLA)-4 and inhibits the translocation of activated VLA-4-expressing leukocytes across the blood-brain barrier into the central nervous system. (Polman et al., 2006; McCormack, 2013) Marked eosinophilia (defined as >1.0 G/l) was described in up to 10–19% of patients treated with NTZ. (Abbas et al., 2011; Florek et al., 2010) However, data on probability and frequencies of clinical manifestations of hypereosinophilic syndromes with organ involvement under treatment with NTZ are sparse. So far, only two case reports of eosinophilic pneumonia and a single case report of each eosinophilic dermatitis and eosinophilic fasciitis during NTZ treatment have been described. (Curto et al., 2016; Yasuda et al., 2019; Bujold et al., 2014; André et al., 2010).

The aim of our retrospective observational study was to describe the frequency of mild and marked eosinophilia and associated clinical symptoms with the help of our pharmacovigilance system in a large retrospective cohort of natalizumab treated RRMS patients since July 2016. Moreover, our hypereosinophilic syndromes will be added to those published in the literature with the aim to identify parameters associated with clinical symptoms of natalizumab induced eosinophilia.

2. Methods

The retrospective study was approved by the local ethic committee (No 2017–01369, last amendment in November 2019). Patient data were extracted from the patient information system of our infusion ward using the search algorithm “natalizumab” or “Tysabri” and “Multiple sclerosis” or “Multiple sclerosis” alone. Hereby we identified 132 consecutive NTZ treated MS patients in our center since July 2016. Afterwards all eosinophil counts of those patients were extracted from laboratory records leading to a final cohort of 115 patients with at least one measurement of eosinophil granulocytes in peripheral blood and in total 621 measurements since July 2016. In our center, we perform an analysis of whole blood count, ALAT, gamma-GT, sodium, potassium, creatinine and C-reactive protein in every patient on natalizumab before initiation of therapy, after 4 months and from there on every 6 months. However, 17 patients had no measurement of eosinophil counts in our center (as they were performed at the general practitioner) and were therefore excluded. Patients with mild eosinophilia (defined as eosinophil granulocytes >0.4 G/l, but <1 G/l) and marked eosinophilia (defined as eosinophil granulocytes >1 G/l(Florek et al., 2010)) were

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https://doi.org/10.1016/j.jneuroim.2021.577505
Received 3 December 2020; Received in revised form 22 January 2021; Accepted 27 January 2021
Available online 30 January 2021

subsequently identified in this cohort. Additionally, we identified 116 untreated RRMS patients since July 2016 at least one measurement of eosinophil granulocytes in peripheral blood, analyzed the laboratory records and compared those with the NTZ treated MS patients. Patient records of these cases were then manually checked by neuroimmunologic consultants (RH, CF, LD) for clinical symptoms during blood eosinophilia.

2.1. Literature review

PubMed database was searched twice by (CF, RH, LD) using the search terms "eosinophilic/eosinophilia natalizumab" and "eosinophilic/eosinophilia Tysabri" (date of last PubMed search 29.10.2020). Hereby 9 articles (Abbas et al., 2011; Florek et al., 2010; Curto et al., 2016; Yasuda et al., 2019; Bujold et al., 2014; André et al., 2010; Rocher et al., 2010; Mihalova et al., 2015; Beales, 2019) dealing with blood eosinophilia with and without clinical symptoms during natalizumab treatment were identified. We compared the data of those studies to our own data and analyzed all reported cases of asymptomatic and symptomatic eosinophilia in NTZ treated patients.

2.2. Statistic

Continuous variables were presented as mean and 95% confidence interval (95%CI) (where applicable) or as median and 25th/75th percentile and compared using the non-parametric Mann-Whitney *U* test or the Kruskal-Wallis-Test in independent samples. Categorical variables were reported as frequencies and compared with Chi^2 test (where applicable) or the Fisher-Yates (exact Fisher) test.

3. Results

3.1. Untreated compared to natalizumab treated MS patients

We identified in our institution since July 2016 a cohort of 115 natalizumab (NTZ) treated RRMS patients and 116 untreated RRMS patients with at least one measurement of eosinophil counts in peripheral blood (Fig. 1). Mean age and sex distribution of untreated and NTZ treated RRMS patients were evenly distributed (age NTZ: 41.9 years (95%CI 39.4–44.4 years) vs age untreated 39.4 years (95%CI 37.3–41.4 years), p-value = 0.30; female sex NTZ: 85/115 vs female sex untreated: 77/116, p-value = 0.29). 112/116 untreated RRMS patients (97%) had normal eosinophil counts and the remaining 4/116 (3%) showed mild eosinophilia (Table 1). Eosinophilia occurred significant less frequently in untreated RRMS patients compared to NTZ treated RRMS patients (mild eosinophilia: 37/115 patients (32%); marked eosinophilia 7/115 patients (6%); p-value<0.001, Table 1, Fig. 1).

3.2. Natalizumab induced eosinophilia

Patient records of all patients with blood eosinophilia were manually checked by neuroimmunologic consultants (RH, CF, LD) for clinical symptoms during blood eosinophilia and other possible reasons for blood eosinophilia like allergies, helminthiasis, or other diseases. Mean observed NTZ treatment duration was 61.2 months (25th-75th percentile 31–88 months). Any eosinophilia occurred in 44/115 NTZ treated RRMS patients and age distribution did not differ in patient groups classified by presence and severity of eosinophilia (Kruskal-Wallis-test p-value = 0.402, Table 2). Regarding sex distribution, a trend towards a higher percentage of female sex in NTZ treated RRMS patients with eosinophilia was observed (p-value = 0.045). Median time to first eosinophilia in all 44 NTZ treated patients was 49.5 months (25th-75th percentile 24.3–76.8 months), whereas median time to maximal eosinophilia was 53 months (25th-75th percentile 28.8–78). In those NTZ treated RRMS patients with eosinophilia, median time until 1st blood eosinophilia as well as median time until maximal eosinophil count were not shorter in patients with marked eosinophilia compared to patients with mild eosinophilia (1st blood eosinophilia, p-value = 0.148; maximal eosinophilia: p-value = 0.205; Table 2). As mentioned above, in our center we perform an analysis of whole blood count, ALAT, gamma-GT, sodium, potassium, creatinine and C-reactive protein in every patient on natalizumab before initiation of therapy, after 4 months and from there on every 6 months. If a patient displays abnormal values at these checks, we usually perform more regular laboratory exams. Except one patient (1/44) detailed below, all other patients with any eosinophilia under treatment with NTZ remained asymptomatic.

3.3. Case report of the patient with clinical symptoms of natalizumab induced eosinophilia

Our symptomatic patient is a 39-year-old nonsmoking woman with RRMS diagnosed in August 2018. Oligoclonal Bands type 2 and cerebral magnetic resonance imaging (MRI) scans supported the diagnosis of a RRMS (Fig. 2) and we found no alternative diagnosis. Treatment with natalizumab was started in August 2018. In October 2018, after 2 infusions of natalizumab, she developed fever and a productive cough. Her general practitioner started an antibiotic treatment with amoxicillin/clavulanic acid and inhaled steroids, as the X-ray of the chest showed reticular opacities in the upper left side of the lung (X-ray not shown). In December 2018 (after 4 infusions of natalizumab) she presented in our neuroimmunologic outpatient department for the regular control and she complained about chronic coughing. She reported no arthralgia, no asthma or oral ulcers. In the blood samples a marked eosinophilia (maximal value 2.89 G/L, range 0.1–2.89 G/l, range of normal 0.02–0.4 G/L, $n = 9$; maximal value of leucocytes 20.8 G/l, range 7.17–20.8 G/l, range of normal 3.00–10.5 G/l, $n = 11$), with slightly elevated C-reactive protein (CRP) (12 mg/l) was found. A pulmonary computed tomography (CT) scan showed multiple lung masses with aerobronchograms and a lesion in the upper right lobe (Fig. 3A). Tests for autoimmune diseases, connective tissue diseases, and vasculitis showed an anti-neutrophil cytoplasmic antibodies (ANCA) titer of 1:320 (range < 1:80) with elevated PR3-ANCA (95.1 IU/ml, range < 5 IU/ml); whereas antinuclear antibodies, anti-DNA, anti-Sm, anti-ribonucleoprotein, anti-Ro, anti-La, anti-centromere, anti-SCL 70, anti-Jo1, anti-citrullinated peptide, and rheumatoid factor remained negative. The pulmonary CT scan showed no lymphadenopathy, and in the cranial MRI there were no signs of an infectious process. In the follow-up pulmonary CT scan, after re-exposition to natalizumab in March 2019, a worsening with extensive bilateral consolidations could be seen, but still no signs of lymphadenopathy or granuloma (Fig. 3B). The bronchoscopy did not demonstrate endobronchial lesions, whereas the bronchoalveolar lavage and the biopsy showed a lymphohistiocytic inflammatory cell infiltrate with eosinophilic granulocytes, but no acute purulent inflammation. Cultures for bacteria, mycobacteria, fungi, and studies for parasites and virus remained negative. The resulting diagnosis was "pulmonary eosinophilia associated with natalizumab treatment". Despite the increased PR3-ANCA values, we found no clinical, laboratory or radiological sign for an eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, microscopic polyangiitis or anti-glomerular basement membrane autoantibody disease. We found no signs of a drug-induced ANCA-associated vasculitis, where usually MPO-ANCA and not PR3-ANCA are encountered and NTZ has not been described as a possible offending agent (Pendergraft 3rd and Niles, 2014). We found no correlation of elevated ANCA values to natalizumab in literature. We stopped the therapy with natalizumab and started systemic corticosteroids (1 mg/kg body weight) and subsequently Ocrelizumab in December 2019. At the last follow-up visit in January 2020, the patient was asymptomatic, the laboratory examination showed a normal eosinophilic count and the pulmonary CT scan showed an almost complete resolution of the pulmonary infiltrates (Fig. 3C).

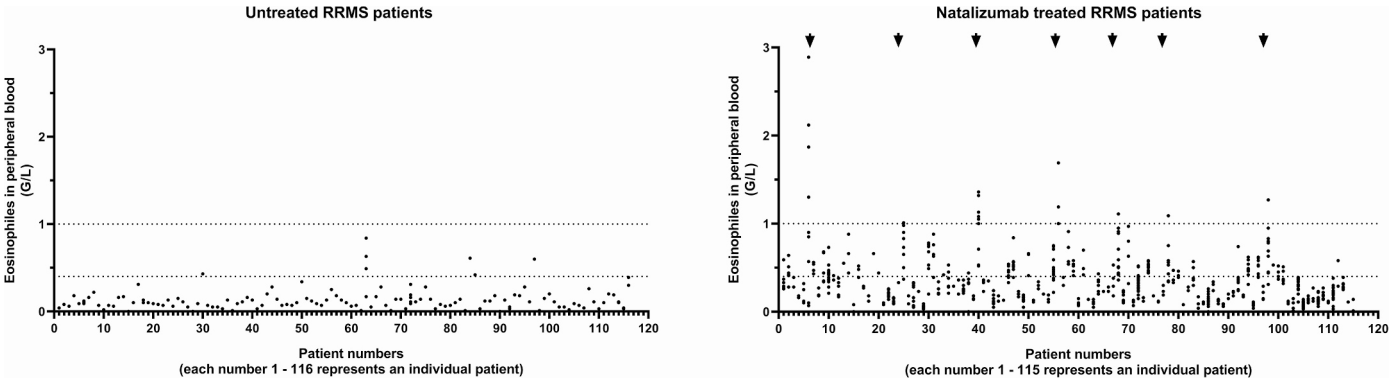

Fig. 1. Eosinophil counts in peripheral blood of untreated and natalizumab treated RRMS patients. Abbreviations: RRMS: relapsing remitting multiple sclerosis; G/l: giga/l; arrows denote patients with marked eosinophilia.

Table 1
Eosinophilia in NTZ treated and untreated RRMS patients. Abbreviation: NTZ: natalizumab; RRMS: relapsing remitting multiple sclerosis.

Eosinophilia				
	No	Mild	Marked	p-value
No treatment	112	4	0	
NTZ	71	37	7	<0.001

Table 2
Baseline characteristics of NTZ treated patients without, with mild and with marked eosinophilia.

Baseline characteristics of NTZ treated patients without eosinophilia					
	Mean	95% CI	Median	25th/75th percentile	*n*
Age all (years)	39.5	36.9–42.2			71
Age female (years)	38.7	35.5–42			53
Age male (years)	42	36.9–47.1			18
Observed treatment all (months)			60	31/88	71
Observed treatment f (months)			61	34.5/88.5	53
Observed treatment m (months)			53	18.5/90.5	18
Baseline characteristics of NTZ treated patients with mild eosinophilia					
Age all (years)	39.9	36.2–43.6			37
Age female (years)	37.1	31.5–42.7			19
Age male (years)	42.8	37.5–48.2			18
Observed treatment all (months)			62	42/88.5	37
Observed treatment female (months)			63	42/85	19
Observed treatment male (months)			61.5	47.3/91.8	18
NTZ treatment to eos all (months)			54	25.5/78	37
NTZ treatment to eos female (months)			54	19/78	19
NTZ treatment to eos male (months)			53	29/82.5	18
NTZ treatment to max eos all (months)			56	36/79	37
NTZ treatment to max eos female (months)			56	27/78	19
NTZ treatment to max eos male (months)			53	29/82.5	18
Baseline characteristics of NTZ treated patients with marked eosinophilia					
Age all (years)	34.4	25.2–43.7			7
Age female (years)	38.8	28.8–48.8			5
Age male (years)	23.5	n/a			2
Observed treatment all (months)			47	24/80	7
Observed treatment female (months)			24	16/103	5
Observed treatment male (months)			50	n/a	2
NTZ treatment to eos all (months)			30	2/58	7
NTZ treatment to eos female (months)			19	1.5/74.5	5
NTZ treatment to eos male (months)			31.5	n/a	2
NTZ treatment to max eos all (months)			34	16/63	7
NTZ treatment to max female (months)			22	12/86	5
NTZ treatment to max male (months)			36.5	n/a	2

Abbreviations: 95% CI: 95% confidence interval; eos: eosinophilia; f: female; m: male; max: maximal; n/a: not applicable; NTZ: natalizumab.

3.4. Review of the literature

Reviewing the scientific literature leads to identification of 4 additional case reports of natalizumab treated RRMS patients with symptomatic eosinophilia (Curto et al., 2016; Yasuda et al., 2019; Bujold et al., 2014; André et al., 2010) and 3 cases with asymptomatic marked eosinophilia with cell counts >1 G/l (Abbas et al., 2011). In our single center cohort we found 1 case of symptomatic eosinophilia, 6 cases of asymptomatic marked eosinophilia and 37 cases of mild eosinophilia (which all remained asymptomatic) of in total 115 NTZ treated RRMS patients with at least one eosinophil count since July 2016. So far, there were no NTZ treated patients with mild eosinophilia described in literature.

This leads to a total case count of 51 NTZ treated RRMS patients with eosinophilia (consisting of our own 44 patients and 7 patients described in literature). Eosinophil counts of all 51 symptomatic and asymptomatic patients ranged from 0.41 G/l to 5.52 G/l and were in mean 1.1 G/l (95%CI 0.79–1.41). Mean age of all patients was 39.1 years (95%CI 34.1–42.1 years). The 46 asymptomatic patients had a mean eosinophil count of 0.92 G/l (95%CI 0.65–1.18 G/l), whereas the 5 symptomatic patients had a significantly higher mean eosinophil count of 2.75 G/l (95%CI 0.71–4.79 G/l, p-value<0.001). Three of five (60%) symptomatic patients were female, whereas 26 of 46 (57%) asymptomatic patients were female (p-value = 0.63). In symptomatic patients, symptoms were pneumonia ($n = 3$ (1,7 and our case)), fasciitis ($n = 1$ (Rocher et al., 2010)) and dermatitis (n = 1 (Mihalova et al., 2015)). Eosinophilia in symptomatic and asymptomatic patients started between 1 month and 114 months after initiation of NTZ (median 36 months, 25th-75th percentile 12–68 months). Eosinophilic disease started between 1 and 12 months after initiation of NTZ (median 2 months; 25th75th 1–9 months), whereas asymptomatic eosinophilia was found significantly later between 1 and 114 months after initiation of NTZ (median 47 months; 25th-75th percentile 19–74.3 months, p value = 0.004).

4. Discussion

Natalizumab is commonly used as treatment in RRMS. It is commonly well tolerated, but a rarely described adverse effect of Natalizumab seems to be a symptomatic or asymptomatic eosinophilia. (Abbas et al., 2011; Curto et al., 2016; Yasuda et al., 2019; Bujold et al., 2014; André et al., 2010; Rocher et al., 2010).

In the literature, eosinophilia is described in 10–19% of patients under treatment with natalizumab (Abbas et al., 2011; Florek et al., 2010). We found no data of cohort analyses regarding the frequency of symptomatic eosinophilia under treatment with natalizumab, hence our work delivers the first such data set so far. In our cohort of 132 RRMS patients under treatment with natalizumab since July 2016, we had at least one eosinophil counts of 115 patients (87% of all patients). Of those 115 patients, 7 patients had a marked eosinophilia (6% of all patients with eosinophil counts) and only one of those (0.9% of all patients with eosinophil counts) was symptomatic. Another 37 treated patients (32%) showed mild eosinophilia, which all remained asymptomatic. In conclusion, in our single center cohort, 44 of 115 natalizumab treated RRMS (38%) patients showed an eosinophilia, which is higher than the reported frequency in the literature and remained in 99% of cases without clinical symptoms. Some studies suggest that natalizumab may cause peripheral hypereosinophilia in a subset of patients. The observation of these subgroups shows a close relationship between natalizumab and eosinophilia, which emerges a few weeks after treatment initiation, disappears after drug discontinuation, and reappears after natalizumab re-exposition. (Abbas et al., 2011; Rocher et al., 2010) The risk factors and exact mechanisms leading to marked hypereosinophilia under natalizumab treatment remain unknown, an association with Th2 immune responses was discussed. (Abbas et al., 2011).

In our cohort, we first found eosinophilia in natalizumab treated patients after a median treatment duration of 49.5 months (25th-75th

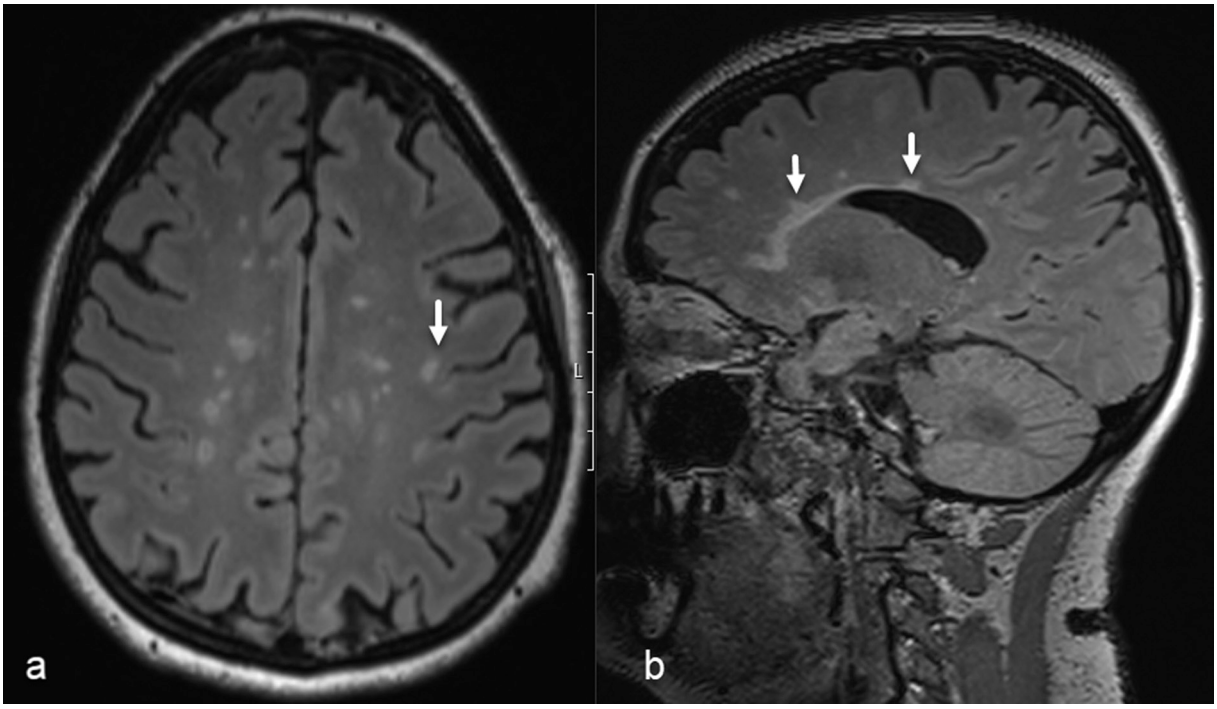

Fig. 2. A: Axial FLAIR-weighed MR scan showing multiple hyperintense lesions in the deep white matter and a juxtacortical lesion (arrow). Abbreviations: FLAIR: Fluid attenuated inversion recovery; MR: magnetic resonance.
B: Sagittal FLAIR-weighed MR scan showing multiple hyperintense periventricular lesions (arrows). Abbreviations: FLAIR: Fluid attenuated inversion recovery; MR: magnetic resonance.

percentile: 24.3–76.8 months), whereas median time to maximal eosinophilia was 53 months (25^{th}-75^{th} percentile, 28.8–78 months). However, severity of eosinophilia was related to clinical symptoms, as patients with eosinophilic disease had significant higher eosinophil counts than those who remained asymptomatic. Further, a symptomatic eosinophilia developed in all documented cases within one year of NTZ treatment and the lung was most often affected highlighting the potential threat of NTZ induced eosinophilic disease.

The main limitation of our study is the retrospective nature and single center design. However, as eosinophil counts were available in more than 80% of the identified consecutive natalizumab treated MS patients, our cohort can be regarded as a representative sample for Caucasian RRMS patients. As we perform an analysis of whole blood count, ALAT, gamma-GT, sodium, potassium, creatinine and C-reactive protein in every patient on natalizumab before initiation of therapy, after 4 months and from there on every 6 months, a selection bias is unlikely. Another limitation are the positive PR3-ANCA values of our patient with the eosinophilic pneumonia, where we cannot rule out a causal relation. However, this has not been described in literature so far.

In conclusion, our work sheds light on a seemingly rare and so far little discussed aspect of treatment with natalizumab. Even though the eosinophilia seems to become rarely symptomatic, it is highly relevant to spread the knowledge of this adverse effect of natalizumab, as natalizumab has to be stopped to treat this potentially severe condition. Further studies on drug safety in real life settings are warranted to better describe drug associated toxicity and adverse effects.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and material

Data and material are available upon reasonable request via the corresponding author.

Code availability

Not applicable.

Authors contributions

Diem L was responsible for conceptualization, data curation, formal analysis, writing - original draft and review & editing.

Hoepner R was responsible for conceptualization, data curation, formal analysis, supervision and writing - original draft and review & editing.

Bagnoud M contributed to conceptualization, visualization and writing - review & editing.

Hoepner R has received research and travel grants from Roche, Novartis and Biogen Idec and speaker p0165 from Biogen, Novartis, Merck, Celgene and Almirall, not related to this work. He reports no conflicts of interest related to this manuscript.

Salmen A contributed to conceptualization and writing - review & editing.

Chan A contributed to conceptualization and writing - review & editing

Friedli C was responsible for conceptualization, data curation, investigation, methodology, visualization, formal analysis, and writing - original draft and review & editing

Conflicts of interest and authors disclosures

Bagnoud M reports no disclosures or conflicts of interest in relation to this manuscript.

Diem L has received travel grants from Bayer, Biogen, Roche, and Merck, as well as speaker honoraria from Merck and Biogen, not related to this work. She reports no conflicts of interest related to this manuscript.

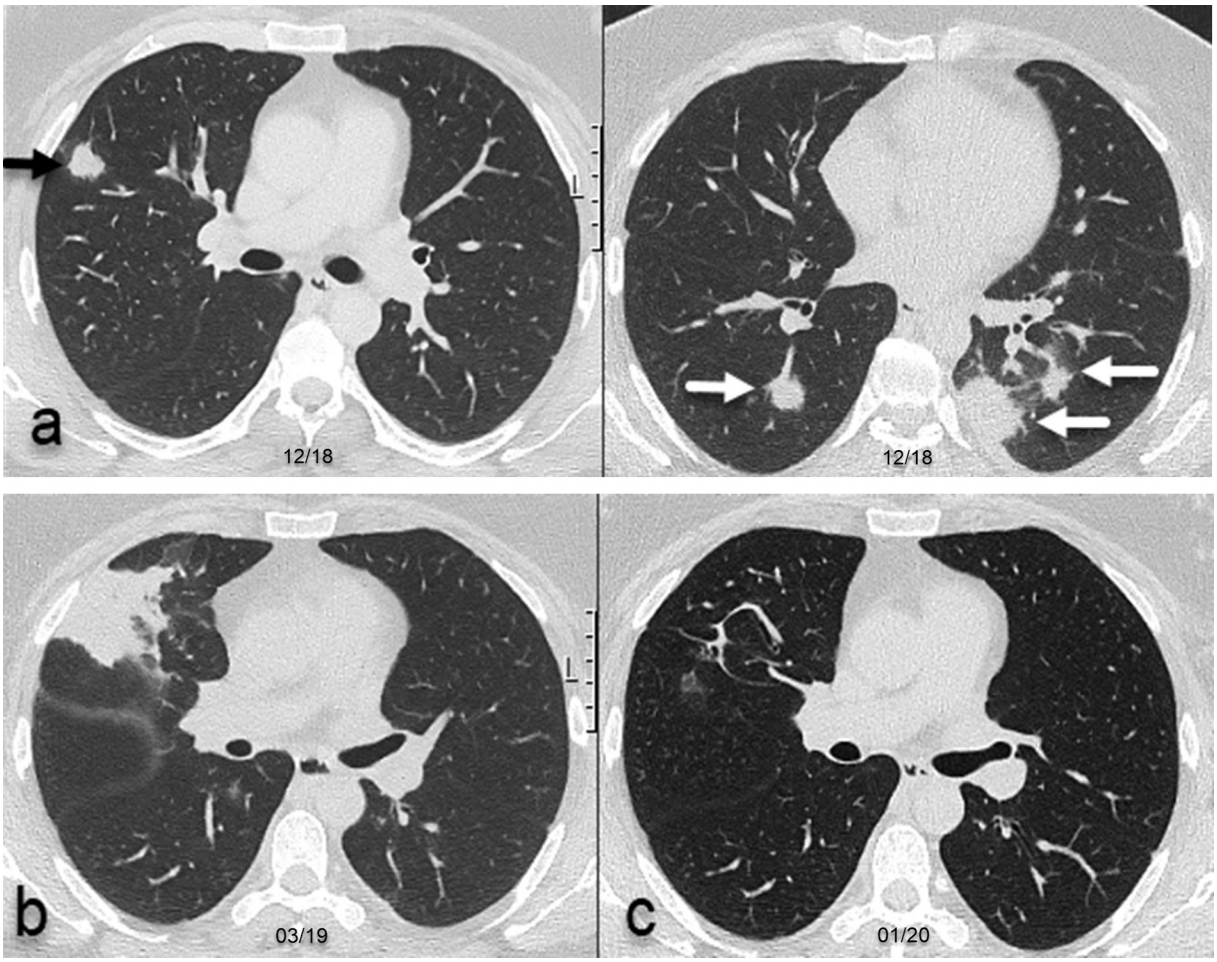

Fig. 3. A: Axial pulmonary CT scan showing multiple lung masses with aerobronchograms and a lesion in the upper right lobe. Abbreviation: CT: Computer tomography.
B: Axial pulmonary CT scan showing worsening with extensive bilateral consolidations. Abbreviation: CT: Computer tomography.
C: Axial pulmonary CT scan showing partial resolution of the pulmonary infiltrates. Abbreviation: CT: Computer tomography.

Friedli C has received travel grants from Biogen and Sanofi Genzyme, as well as speaker honoraria from Biogen and Merck, not related to this work. He reports no conflicts of interest related to this manuscript.

Hoepner R has received research and travel grants from Roche, Novartis and Biogen Idec and speaker honoraria from Biogen, Novartis, Merck, Celgene and Almirall, not related to this work. He reports no conflicts of interest related to this manuscript.

Salmen A has received speaker honoraria and/or travel compensation for activities with Almirall Hermal GmbH, Biogen, Merck, Novartis, Roche and Sanofi Genzyme, and research support of the Swiss MS society not related to this work. She reports no conflicts of interest related to this manuscript.

Chan A has served on advisory boards for, and received funding for travel or speaker honoraria from, Actelion-Janssen, Almirall, Bayer, Biogen, Celgene, Sanofi-Genzyme, Merck, Novartis, Roche, and Teva, all for hospital research funds; and research support from Biogen, Genzyme and UCB. Chan A is associate editor of the European Journal of Neurology and serves on the editorial board for Clinical and Translational Neuroscience and as topic editor for the Journal of International Medical Research. He reports no conflicts of interest related to this manuscript.

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