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CASE REPORT

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Diagnostic challenges in pulmonary lymphomatous spread mimicking ARDS in an AIDS patient: a case report

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Abstract

Background Immunocompromised individuals, particularly those with AIDS, are at increased risk of developing lymphoproliferative tumours and opportunistic infections. Radiologic findings alone may not always distinguish between these entities.

Case presentation We describe the case of a patient with acquired immunodeficiency syndrome (AIDS) with rapidly worsening dyspnoea and clinical signs suggestive of acute respiratory distress syndrome (ARDS). Despite initial concerns for ARDS, autopsy revealed an advanced-stage, aggressive lymphoma as the underlying cause. This case highlights the challenge of differentiating ARDS from lymphoma in AIDS patients, especially when atypical radiologic findings, such as nodular opacities, are present.

Conclusions The diagnosis of ARDS relies on imaging, oxygenation abnormalities, and clinical timing. However, various infectious and non-infectious conditions can mimic ARDS, making an accurate differential diagnosis essential. This case adds to the literature by underscoring the importance of considering lymphoproliferative disorders in AIDS patients presenting with respiratory distress, especially in the absence of typical lymphoma-related symptoms.

Keywords ARDS, AIDS, Immunosuppression, Ground glass opacities, Diffuse large B cell lymphoma

Background

The Acute Respiratory Distress Syndrome (ARDS) can be recognized based on some easily detectable biochemical and imaging findings [1, 2]; however, it is an umbrella diagnosis lumping together clinical conditions ranging from pulmonary infections to inflammatory, autoimmune and neoplastic diseases, each requiring an appropriate treatment [3, 4]. Actually, as pulmonary and extra pulmonary infections mainly account for its occurrence, other causes can go overlooked. This particularly applies in cases in which the clinical history and the history and microbiological findings cooperate to indicate an infectious cause of the ARDS, possible leaving on ten background other differential diagnoses. However, a high level of suspicion is warranted in patients not responding to

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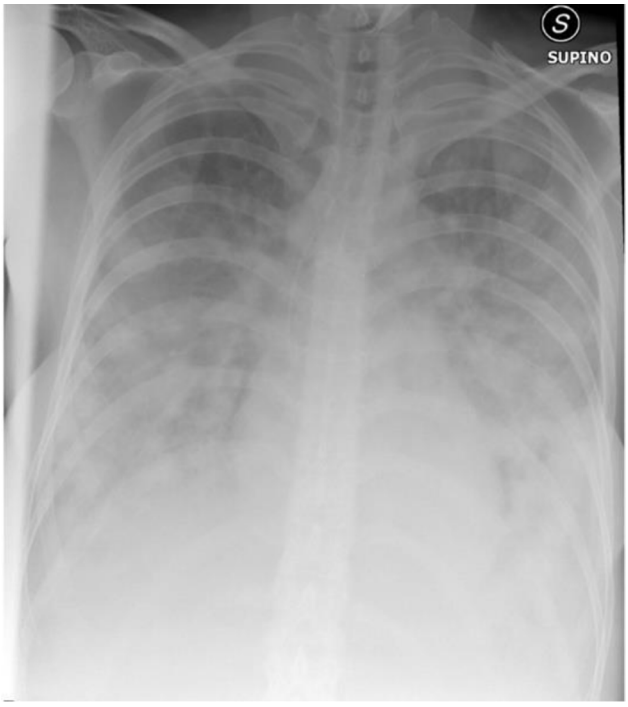

Fig. 1 Chest-X-ray obtained in supine position at the admission at the Emergency Department showed diffuse bilateral parenchymal consolidation, predominantly peripheral in the lower lobes and pleural effusion

the current treatments of ARDS because not all diffuse and bilateral pulmonary opacities are due to the accumulation of fluid and/or cellular debris into the alveolar spaces.

Case presentation

A 44-year-old woman presented to our Emergency Department due to fever, cough and dyspnoea started five days before. The history revealed a substance abuse ceased 6 years ago; at that time, she resulted also HIV + and HCV + but refused any treatment. Since then, till the current hospitalization, the patient did not seek medical attention. At the admission, the patient appeared drowsy with a rapid and shallow breathing pattern (respiratory rate = 40 breaths/min); the temperature was 37,5 °C, the arterial pressure was 80/50 mm Hg and the heart rate was 125 beats/min. The auscultation revealed diffuse bilateral crackles and rhonchi; other physical signs were normal. An arterial blood gas analysis obtained while breathing with a Venturi Mask at a $FIO_2 = 0,6$ demonstrated a severe hypoxemia ($PaO_2/FIO_2 = 113$). A Chest-X-ray (CXR) in the supine position was obtained (Fig. 1), and showed diffuse bilateral parenchymal consolidations, predominantly in the periphery of the lower lobes associated with pleural effusion; these findings were suggestive for an acute respiratory distress syndrome (ARDS). A trial of non-invasive ventilation at a FIO_2 0,8 failed to correct the hypoxemia and the patient was intubated and transferred to the Intensive Care Unit (ICU) where a lung protective mechanical ventilation was initiated under sedation and muscle relaxation.

A broncho-alveolar lavage (BAL), blood and urine cultures were obtained; the BAL resulted positive for high-titer Epstein - Barr virus (EBV) DNA associated with rare multi-drug resistant (MDR) *Pseudomonas aeruginosa* colonies whereas the other cultures were negative; i.v. Colistin (loading dose $9 * 10^6$ followed by $4.5 * 10^6$ /day) associated with i.v. Meropenem (g 2* 3/ day) was started. A chest CT was acquired after the i.v. administration of contrast media (Fig. 2). It excluded a necrotizing pneumonia and a pulmonary embolism but demonstrated the presence of diffuse bilateral consolidations and ground glass opacities, especially in the posterior-basal segments of the lower lobes, with a cranio-caudal gradient along with nodular airspace opacities, and pleural effusions were detected. The low CD3 and CD4 T-lymphocyte count and the CD4/CD8 ratio indicated a severe immunodepression (Table 1). On the 2nd day after the ICU admission the CXR was repeated (Fig. 3), showing a significant increase of the previously reported consolidations and pleural effusions.

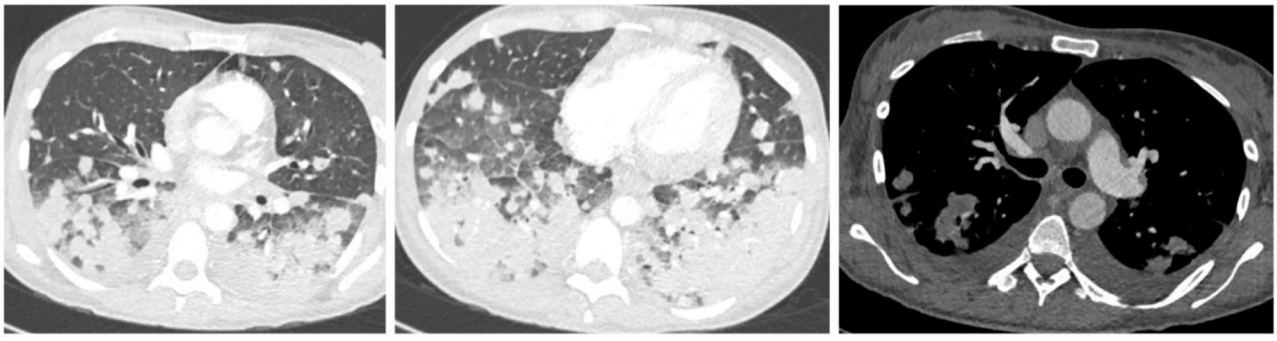

Fig. 2 Chest CT scan acquired after the administration of contrast media excludes the presence of pulmonary embolism and necrotizing pneumonia; the presence of diffuse bilateral consolidation and ground glass opacities especially in the postero-basal segments of the lower lobes with a cranio-caudal gradient were confirmed (Fig. 2); moreover, nodular airspace opacities and pleural effusion were detected

Table 1 Time course of biologic variables

Variable	Normal Range	D1 (admission)	D2	D3	D4
Hemoglobin (g/dl)	12,0–16,0	7,5	8,4	9,0	8,1
Red Blood Cells (* 10^6)	4,20 – 5,00	2,250	2,530	2,650	2,44
White Blood Cells (* 10^3)	4–11	1,18	1,92	2,65	1,84
Platelets (*10^3)	150–400	31	35	17	10
Creatinine (mg/dl)	0,40 – 1,10	1,20	1,18	1,08	1,25
PaO_2/FIO_2	> 400	113	105	95	95
NH_3(mcg/dl)	27–901	91	n.a.	125	158
Total Bilirubin (mg/dl)	0,30 – 1,10	1,85	n.a.	1,88	2,26
C-reactive protein (mg/L)	< 0,5	103,3	130,0	116,9	115,9
Lactate (mg/dl)	6,5–19,3	82,1	68.7	75	85
INR (%)	0,78 – 1,20	1,62	1,46	1,42	1,5
APTTr (%)	0,76 – 1,18	0,78	24,7	0,83	0,91
Fibrinogen (mg/dl)	160–380	139	144	118	115
D-Dimer (mg/L)	> 0,5	5,85	6,00	6,61	6,17
Antithrombin III (%)	78–124	36	30	24	115
CD3 (cell/μl)	605–2460	151	n.r.	n.r.	n.r.
CD4 (cell/μl)	500–1200	21	n.r.	n.r.	n.r.
CD4/CD8*	1,50 – 3,50	0.15	n.a.	n.a.	n.a.
ALT/AST *(U/L)	< 35	76/35	n.a.	64/27	59/22
SAPS II Score	0	61	n.r.	n.r.	n.r.
SOFA Score	0	12	13	15	18

INR: international normalized Ratio; APTTr: indexed Activated Partial Thromboplastin Ratio; n.a.: not available; n.r.: not repeated

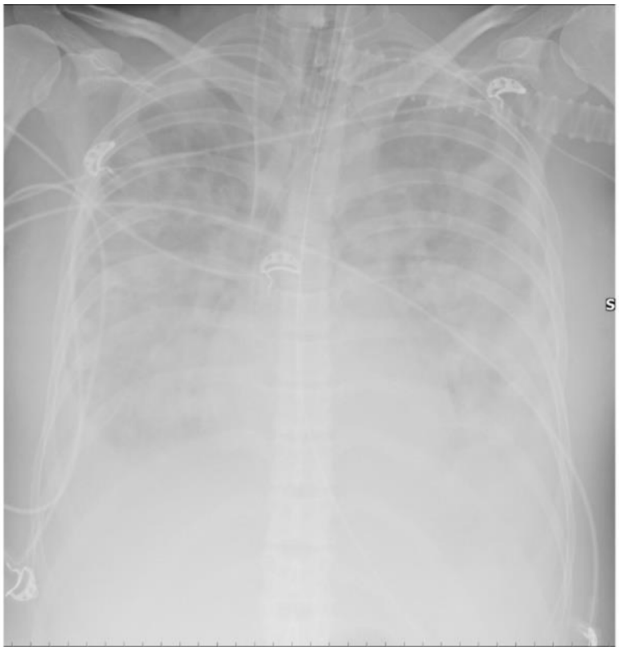

Fig. 3 A follow-up chest X-ray performed 3 days after the admission in ICU, demonstrated a significant increase of the previously reported consolidations and pleural effusion

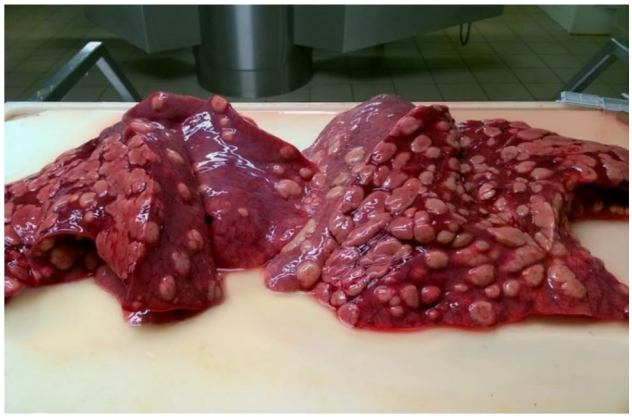

Fig. 4 Many whitish nodules were bilaterally present

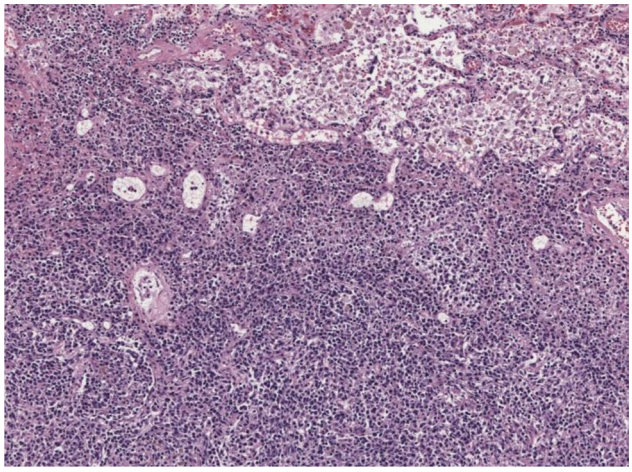

Fig. 5 Lung parenchyma infiltrated by large sized lymphoid cells. The lymphoid proliferation shows a destructive pattern as it substitutes the lung parenchyma (HE x 10)

On the 3rd post-admission day, the arterial pressure dropped and failed to respond to further increase of the vasopressors and, after discussion with her relatives, the patient was switched to comfort measures and died 2 h after the suspension of the vasopressor. An autopsy was performed.

Grossly, the pulmonary parenchyma appeared largely replaced by multiple white nodules (Fig. 4); the non-involved lung was oedematous. The same tissue also invaded the liver and spleen; moreover, the liver showed cirrhosis. On histology, a diffuse proliferation of large sized B-lymphocytes with hyperchromatic nuclei, prominent nucleoli, and a fair amount of cytoplasm was detected infiltrating the lung parenchyma (Figs. 5, 6 and 7). The alveoli showed hyaline membranes deposition and denudation of alveolar walls due to necrosis of type I pneumocytes. Blood vessels were diffusely congested and showed neutrophil aggregation and micro thromboemboli (Fig. 8). Epstein-Barr encoding region (EBER) in situ hybridization was positive. The final diagnosis was

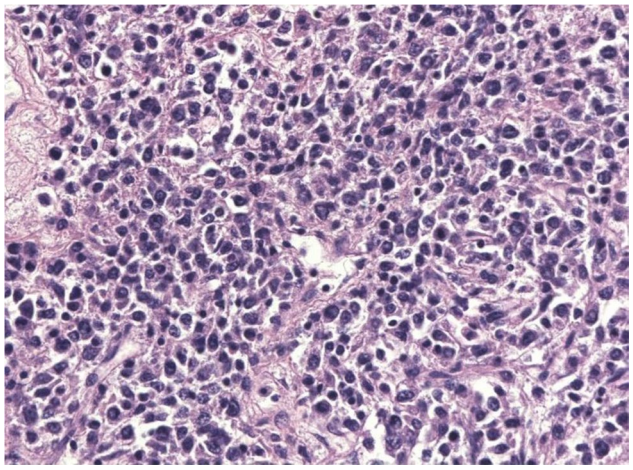

Fig. 6 Higher detail of the large sized lymphoid cells, showing dark nuclei with different shapes and irregular chromatin pattern (HE x 40)

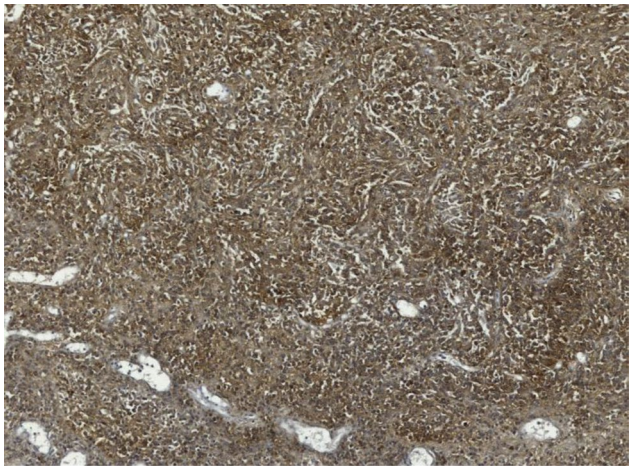

Fig. 7 Large sized lymphoid cells are intensely and diffusely positive to the immunohistochemical staining CD20, indicating a monotonous population of B-lymphocytes (CD20 immunohistochemistry x 10)

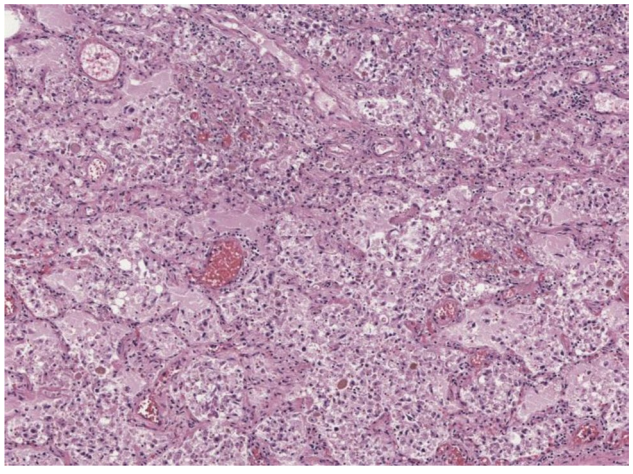

Fig. 8 Denudation of alveolar walls and deposition of hyaline membranes, consistent with diffuse alveolar damage (HE x 10)

EBV-related diffuse large B-cell lymphoma (DLBCL) with severe bi-pulmonary lymphomatous spread, involvement of the liver and spleen, and associated ARDS in HCV + and HIV + patient.

Discussion

Although the more recent definitions of ARDS issued by the European Society of Intensive Care and the Society of Critical Care Medicine are slightly different, the diagnosis of ARDS basically relays on the imaging (bilateral opacities not attributable to other causes), oxygenation abnormalities ($PaO_2/FIO_2 < 300$ with PEEP or CPAP $\geq H_2O$) and timing (< 1 week after a trigger event or the onset of respiratory symptoms) [1, 2].

Actually, a number of clinical conditions caused by either infectious or non-infectious factors fulfil the diagnosis of ARDS making the precise diagnosis crucial [3]. Different factors indicated this diagnosis, including (a) the exceedingly low CD3, CD4 count and the CD4/CD8 ratio making the patient prone to infections due to opportunist pathogens and/or viral reactivation; (b) a septic shock likely due to the *Pseudomonas aeruginosa* found in the BAL that caused a rapidly worsening multiple organ dysfunction syndrome complicated by a liver dysfunction and a DIC [3]; and, finally (c) the poor hemodynamic response to elevated doses of vasopressors indicating an extensive inflammatory reaction [4]. However, this apparently simple diagnosis was not correct, as the multiple confluent opacities demonstrated at the chest x-ray and the lung CT were not inflammatory infiltrates caused by the EBV and *Pseudomonas aeruginosa* but by the diffuse bilateral lymphomatous nodules occupying a large part of the lung parenchyma and involving also the liver and the spleen. For AIDS patients, non-Hodgkin and Hodgkin lymphomas represent the second cause of ICU admission after OI; among them, DLCBL is particularly aggressive and is often associated with EBV infections [5]. The lung parenchyma was largely substituted by the lymphoma and the remaining areas were involved by the ARDS, making the mechanical ventilation unable to correct the abnormal gas exchange. Indeed, the radiologic and clinical findings are consistent with this diagnosis, but the rarity of an ARDS-mimicking lymphoma and the fulminant clinical course drove us on the wrong track, even if it is unlikely that the appropriate treatment would have modified the outcome.

On chest X-ray the presence of air space and interstitial opacities, bilateral and symmetric, are typical but not specific radiological findings of ARDS. Even though chest X-ray remains the first line imaging modality to assess lung disease, CT scan can be helpful in identifying intra or extrapulmonary etiology and to determine the presence of complications (i.e. barotrauma, pulmonary embolism or necrotizing pneumonia) in particular

in patients with discrepancies between clinical and radiological findings [6].

On chest CT bilateral symmetric air space consolidations, in association with ground glass opacities, in the non-dependent lung are suggestive for ARDS, while the presence of bilateral nodules must be correlated with a spectrum of differential diagnosis such as superimposed infection and malignancies, in particular lymphoproliferative disorders in immunocompromised patients [7]. In our patient's case, radiological findings suggestive for ARDS were represented by symmetrically distributed, bilateral, ground-glass opacities and a normal-sized heart would exclude a cardiogenic cause of the symptoms. However, the presence of nodular opacities and pleural effusion should suggest the coexistence of other conditions such as infections caused by fungal or bacterial agents [8]. Furthermore, the presence of consolidative areas in association with diffuse nodules and pleural effusion with no significant mediastinal lymphadenopathy are frequent radiological findings in lymphoproliferative lung disease in immunocompromised patients [9].

Even though pulmonary nodular opacities have been frequently described in immunocompromised patients, CT-scan has a limited value in the differential diagnosis because that nodules size and their distribution are not reliable factors to distinguish an infection from a neoplastic disease [10].

The hyaline membranes and denudation of alveolar walls, together with the vascular changes and inflammatory infiltrate are typical features of the exudative (acute) phase of diffuse alveolar damage (DAD), which is the histologic pattern corresponding to ARDS [11].

The macroscopic findings of multiple confluent whitish nodules in the lungs posed a differential diagnosis between an infectious– possibly granulomatous– disease and a disseminated neoplasm, favouring the latter. The histologic examination confirmed the presence of a neoplasm, which was composed of large, atypical B lymphocytes, consistent with DLBCL.

Lymphomas that develop in HIV + patients are predominantly aggressive B cell lymphomas. They are reported in 4–10% of patients with AIDS, an incidence rate 100 times higher than that of the general population [12]. The most common types include Burkitt lymphoma, diffuse large B cell lymphoma, primary effusion lymphoma (PEL), and plasmablastic lymphoma. There is a significant relationship between lymphoma type and HIV disease status, with Burkitt lymphoma being more common in less immunodeficient patients, with higher CD4 counts ($> 200 \times 106/L$), and DLBCL in patients with long standing AIDS, lower CD4 counts (mean $< 100 \times 106/L$), and higher rate of opportunistic infections [13].

The aetiology is heterogeneous, with several pathogenetic mechanisms proposed, including chronic antigen stimulation, genetic abnormalities, cytokine dysregulation, and concurrent EBV and HHV8 infections. Interestingly, it is reported that EBV + lymphomas have decreased in the era of highly active antiretroviral therapy, which was refused by our patient after the HIV diagnosis. HIV is not directly involved in the malignant transformation of B cells; rather, it is believed that it is chronic immunosuppression that promotes neoplastic growth - possibly facilitated by EBV.

In HIV + patients, lymphomas more frequently present in advanced clinical stage, usually as an extranodal disease with a high tumour burden and bulky disease, involving the gastro-intestinal tract, the central nervous system, the bone marrow or the lungs. The prognosis is generally poor, depending also on the stage at diagnosis and overall patient status.

In our patient, the final diagnosis of DLBCL was mainly driven by morphology. Being an autoptic finding, further typization of neoplastic cells to optimize treatment was considered not necessary.

Conclusions and learning points

- In immunocompromised patients, bilateral ground-glass opacities and nodules on CT require differentiation between ARDS, infection, and malignancy.
- CT alone is insufficient to distinguish infectious from neoplastic nodules; histological confirmation is essential.
- DLBCL should be considered in HIV + patients with pulmonary nodules, especially in advanced immunosuppression.
- HIV-related lymphomas often present at advanced stages with extranodal involvement and poor prognosis, especially without antiretroviral treatment.

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Author contributions
EB interpreted and provided the radiological images and wrote part of the body of the article, especially the case description and discussion from the radiological point of view.GB is the manager of the facility where the patient was admitted, formulated the clinical diagnosis and is the author of part of the introduction, the clinical description and the discussion.MP (corresponding author) provided and commented on the histological images and wrote the discussion regarding the pathological part.RB performed the autopsy and formulated the final diagnosis.

Funding
Nothing to declare.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
This case report describes the story of a patient who ultimately died for the disease and there are currently no close relatives alive. During her hospital stay, she filled out a form in which she consented that her clinical data, including the anonymized images acquired, could be used for clinical research, training and study purposes. We attach the form in the "supplementary material" section.

Competing interests
The authors declare no competing interests.

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