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A progressing inflammatory pulmonary infiltrate in a patient with hyper IgE syndrome

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Abstract

A young man known with autosomal dominant hyper IgE syndrome and changes on his chest radiograph was presumed to be infected with *Aspergillus* and treated with antifungal medicine for 11 months without effect. Positron emission tomography/computed tomography imaging was suggestive of Aspergilloma but bronchoalveolar lavage cultures, cytology as well as biochemistry were negative for Aspergillus. Finally, a transthoracic computed tomography-guided biopsy did not support the diagnosis of fungal infection as only chronic inflammatory changes were found. The patient was treated with Prednisolone after which the changes on his chest X-ray regressed.

Keywords

Infectious diseases, respiratory medicine, allergy/immunology

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Introduction

Hyper IgE syndromes (HIES) are inborn errors of immunity and classified as combined immunodeficiencies with syndromic features. Previously the diagnosis was based on the HIES scoring system based on clinical and laboratory findings, but nowadays the majority of diagnoses of the disorder is confirmed with genetic testing.[1] In the literature, it was originally termed as 'Job's syndrome' due to the skin abscesses that developed in patients with this syndrome who failed to develop redness, warmth and tenderness.

Autosomal-dominant (AD) HIES is an autosomal inherited disease caused by a mutation in the STAT3 transcription factor. It leads to disruption of cytokine signalling in interleukin (IL)-6, IL-22 and Th17 cells. Thus, the immune system is weakened, and the patient becomes vulnerable to infections by extracellular pathogens such as bacteria and fungi.[2,3] Respiratory tract infections are particularly common in this group of patients, especially in childhood.[4] Patients with this disease often have numerous non-infectious characteristics including but not limited to typical facies, retention of primary teeth, hyperextensibility, being prone to bone fractures, cold abscesses on skin and eczema.

In this case report, we describe the case of a patient who suffers from AD-HIES. After his mother had gone misdiagnosed for years as not having the disorder because of a rare variant, she and our patient went through whole genome sequencing and were both found to have the mutations in their STAT3 gene that causes AD-HIES, thereby confirming the diagnosis.[5] The patient had cytokine stimulation and measurement of Th17 cells done. A significant decrease in Th17 cells ($<0.1\%$ of Th cells) and decreased production of IL-17 were seen, further confirming the diagnosis.

Our patient has a mutation in STAT3 c.1406G$>$A (p.Q469R), previously shown to be associated with AD-HIES,[6] confirming the diagnosis. We did not perform functional analysis of the variant as it was described previously.

Case presentation

A 27-year-old male newly diagnosed with AD-HIES with mutation in STAT3 (c.1406A$>$G; c.1406A) was referred to

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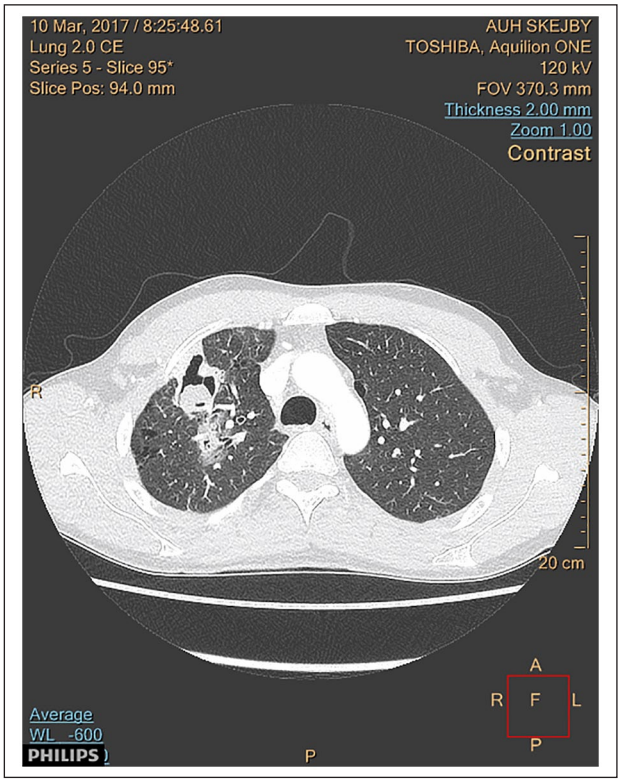

Figure 1. HRCT scan (March 2017).

a pulmonology clinic by the infectious disease clinic, because of incidental finding of large pulmonary infiltrates on his chest X-ray and computed tomography (CT) thorax as well as a cavity with a fungal ball-looking lesion (Figure 1). These radiographic changes were suspicious of pulmonary Aspergilloma.

As a child the patient had suffered from repeated bouts of otitis media, and already as a 6-year-old had suffered from pneumonia confirmed by X-ray imaging. His history included the classic AD-HIES characteristic of retention of primary teeth and typical facies including a wide nose. He had also suffered from fungal nail infections but never fungal infections in any of his mucous linings. He did not suffer from asthma.

In terms of presenting symptoms, the patient had experienced mild productive clear coloured sputum in the mornings for a few years. He had, however, no dyspnoea, weight loss or fever. Pulmonary function tests showed normal dynamic volumes, static volumes and diffusion capacity. A bronchoalveolar lavage (BAL) was performed and the culture was positive for *Streptococcus pneumoniae*, sensitive for penicillin. Cultures also grew *Achromobacter* sp. And polymerase chain reaction (PCR) was positive for *Pneumocystis jirovecii*, which was treated with Sulfatrim. However, BAL was negative for *Aspergillus* sp. and other fungal moulds. PCR and microscopy for *Aspergillus* sp. were negative as well. Biochemically the titre for *Aspergillus* IgG antibody was 0.0 arbitrary unit/mL and therefore negative. Immunological studies showed normal IgG and IgM, but elevated IgA = 6.22 g/L and reduced IgG2 = 1.53 g/L. The Galactomannan antigen test was negative. Furthermore, the BAL showed negative microscopy for *Mycobacterium* sp. The BAL culture for *Mycobacterium* sp. was negative as well. The interferon gamma release assay (IGRA) test was also negative. The value of total serum IgE was slightly elevated at 158 international units (IU)/mL (reference < 115 IU/mL).

The patient was treated with phenoxymethylpenicillin for 10 days because of the BAL findings of *S. pneumoniae* and *Achromobacter* sp. Because of the high suspicion of pulmonary Aspergillosis, empiric Voriconazole treatment was prescribed for 11 months (Figure 2). No tissue biopsy was obtained before initiating treatment. The level of plasma-Voriconazole was monitored throughout the treatment period and found to be within therapeutic levels. A control CT/positron emission tomography (PET) (Figure 3) 2 months later showed increased fluorodeoxyglucose (FDG) uptake at the level of the cavity; 8 months later a high-resolution computed tomography (HRCT) scan (Figure 4) showed further progression of cavitating lesion in the right upper lobe and new infiltrates caudally. A new BAL was performed where *Pseudomonas aeruginosa* was cultured. The second BAL fluid was negative for *Aspergillus* sp., *Mycobacterium* sp. and *Pneumocystis* sp. Blood test was again negative for *Galactomannan* antigen. The patient was given 2 weeks of intravenous (IV) Tazobactam and Ciprofloxacin to eradicate the *P. aeruginosa*. A PET/CT scan was done 3 months later. The pulmonary cavity was unchanged with no PET activity in the perceived fungal ball. However, new pulmonary infiltrates were visible in the right upper lobe. After this, a super-dimension-bronchoscopy with brush biopsies was performed. It came out with normal cells. A CT-guided transthoracic coarse needle biopsy showed chronic inflammation with no evidence of malignancy or any fungal infection.

Finally, as the clinic and all examinations performed did not point towards fungal infection as only signs of chronic inflammation were present and because the radiological findings progressed despite Voriconazole treatment, a new strategy was agreed upon. The patient would now be treated for non-infectious inflammation. The patient was started on prednisolone 25 mg/day (2.5 mg/kg). A control CT thorax (Figure 5) after 1 month of this treatment regimen showed some regression of the infiltrate. A further follow-up CT thorax (Figure 6) 12 months later showed further regression of the infiltrate. The Prednisolone treatment was subsequently stopped (Figure 7). The patient has been followed in the infectious disease clinic ever since, and his condition has been stable. He now runs 5 km a few times a week without any issues. He continues to be treated prophylactically with Sulfatrim and Itraconazole. A follow-up CT thorax in 2021 showed no progression of infiltrate. During the 4 years of follow-up the cavity with a fungal ball looking appearance in the right lung had only regressed from 21 mm in 2017 to 19 mm in 2021. A follow-up IGRA test in 2022 was negative

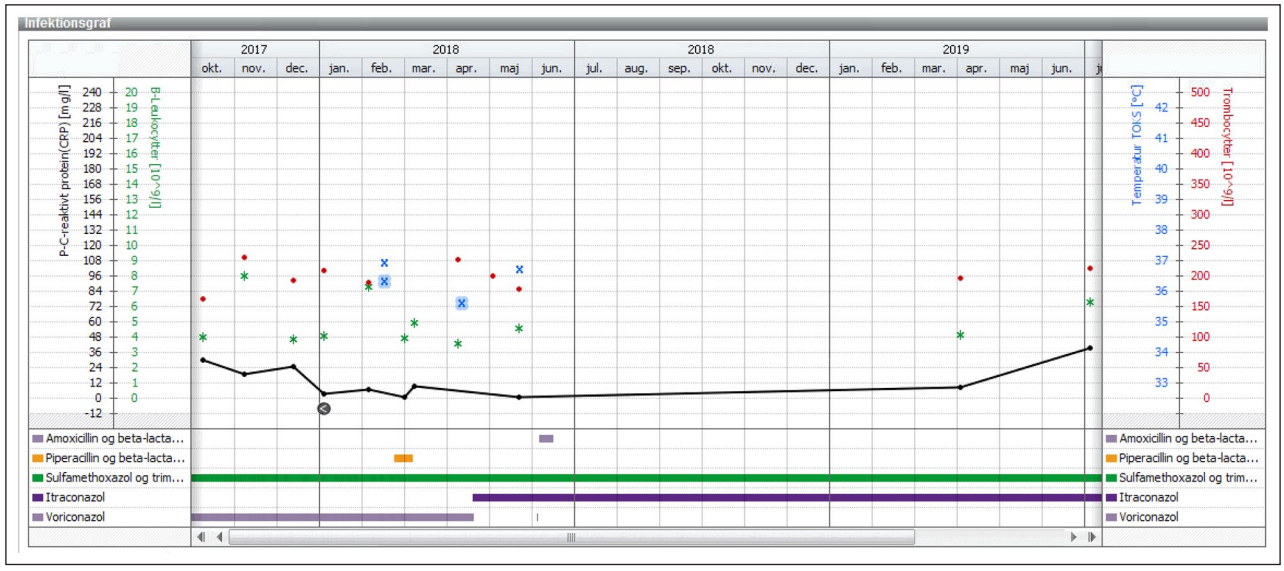

Figure 2. Graph showing voriconale treatment and correlation with C-reactive protein over time.

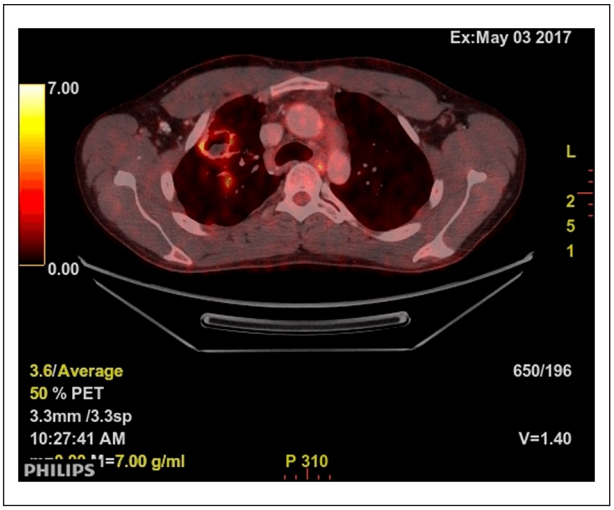

Figure 3. CT/PET image showing high FDG uptake in the right-sided infiltrate (May 2017).

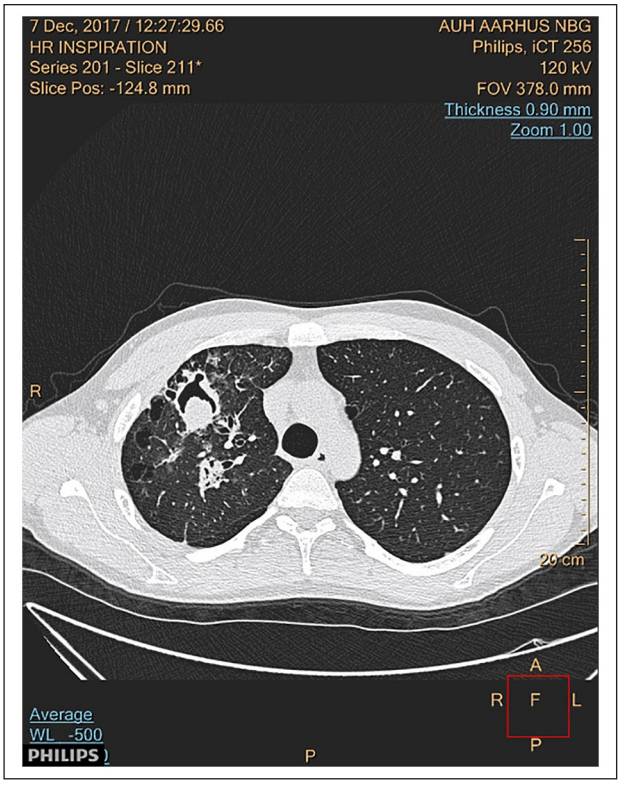

Figure 4. CT scan showing progressing infiltrate (Dec 2017).

for *Mycobacterium tuberculosis* with a positive control (mitogen-nil = 10.00 kIU/L and nil = 0.10 kIU/L).

Investigations

Invasive investigations

Apr 2017 BAL: positive cultures for *Pneumococcus* sp., *Achromobacter* sp., *Pneumocystis* sp.; negative for *Aspergillus* sp. Cytology showed inflammation with macrocytosis and granulocytosis. No tumour cells were seen.

Apr 2017 BAL: negative microscopy for *Mycobacterium* sp., negative cultures for *Mycobacterium* sp.

Feb 2018 BAL: negative cultures. Negative for *Aspergillus* sp. Cytology unchanged from April 2017.

Apr 2018: superdimension-bronchoscopy with brush biopsies: normal cells.

May 2018: CT-guided transthoracic coarse needle biopsy: chronic inflammation, no malignant cells. No fungal cells.

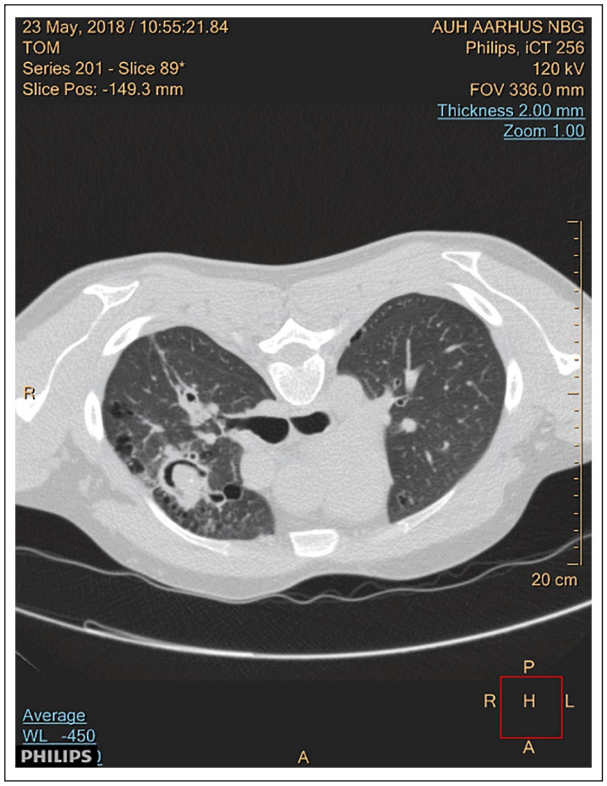

Figure 5. HRCT scan with partial resolution after treatment with oral glucocorticoids (May 2018).

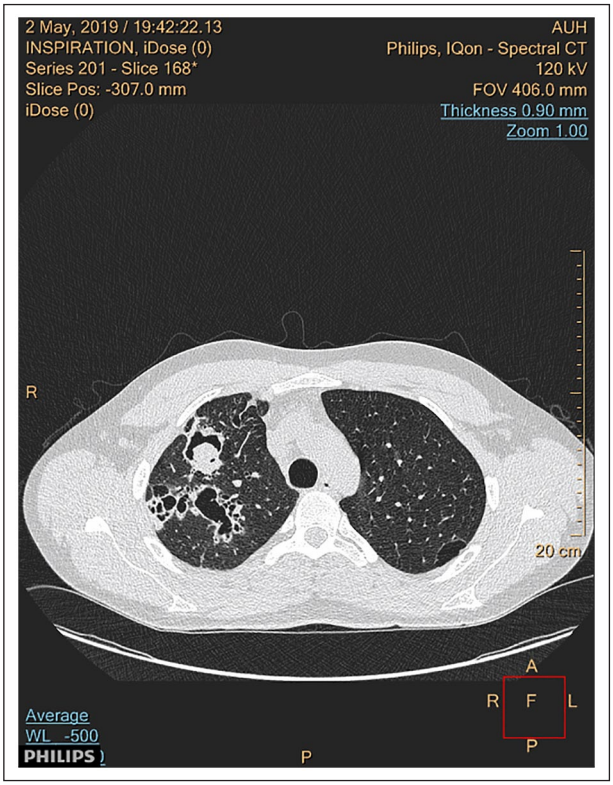

Figure 6. HRCT with further resolution of infiltrative changes (May 2019).

Non-invasive investigations

Mar 2017: HRCT: multiple cavitating lesions in the right upper lobe.

May 2017: PET/CT: multiple cavitating processes in the right upper lobe with high FDG uptake. New infiltrative changes posteriorly and caudally to the known cavity, possible progression of known lesion.

Dec 2017: HRCT: discrete regression of cavitary lesion in right upper lobe. Regression of scattered areas of ground glass opacity.

May 2018: CT: multiple cavitating as well as solid and semisolid changes in the right upper lobe with increased FDG uptake.

May 2019: HRCT: regression of known right-side infiltrate.

May 2020 (HRCT) and May 2021 (CT): unchanged status.

June 2021: lymphocyte-population investigation (Th17-assay): Reduced amount of Th17-helper cells (<0.1% of all T-helper cells).

Differential diagnosis

Aspergillosis.

Cancer.

Various infections.

Mycobacterial infection.

Allergic bronchopulmonary aspergillosis.

Treatment

The patient was treated for 11 months with Voriconazole 400 mg × 2 without effect. 10 days of Phenoxymethylpenicillin 800 mg × 3. Finally treated with Prednisolone 25 mg × 1 with subsequent regression of chest radiograph changes.

Outcome and follow-up

One month after starting Prednisolone chest X-ray imaging showed some regression of right upper lung changes.

Discussion

In a patient known to have AD-HIES the incidental finding of infiltrates and a fungal ball lesion on lung imaging presents a challenge. We argue that the presumptive diagnosis of Aspergillosis was reasonable due to the radiological finding highly suggestive of Aspergilloma along with a priori knowledge that patients with AD-HIES are particularly vulnerable

Figure 7. Graph showing Prednisolone treatment and correlation with leukocytes, neutrophils and lymphocytes over time.

to infections with *Aspergillus* sp. We therefore argue that the decision to initiate treatment was warranted in order to prevent spread of the infection and further harm to the patient.[7]

Once you have identified radiological changes that are highly suspicious of Aspergilloma the diagnostic work-up of Aspergillosis includes using the *A. fumigatus*-specific IgG or IgA blood test. If antibodies are negative, bronchoscopy should be performed to obtain respiratory fluids in order to culture the *Aspergillus* sp. and to obtain a positive PCR result. Galactomannan from BAL fluid also has diagnostic value. Diagnosis can also be obtained with transthoracic aspiration of the cavity with a positive *Aspergillus* sp. culture. Finally, a biopsy of the cavity can also be performed and will often show *Aspergillus* hyphae. The biopsy can also be helpful in excluding other conditions such as malignancy.[8]

The standard treatment for pulmonary Aspergillosis is with oral triazoles such as Itraconazole, Voriconazole or Posaconazole. The treatment should last a minimum of 6 months. Repeat CT scans should be performed at regular intervals to monitor treatment efficacy. If treatment with triazoles fails, one can attempt IV treatment with Amphotericin B or echinocandins. Patients with hyper IgE syndrome often experience recurrent pneumonias which can lead to bronchiectasis or pneumatocele. This makes them susceptible to infections with *Aspergillus* sp. Patients with hyper IgE syndrome tend to have prolonged duration of therapy. Some will require surgery. Complication rate is high.[9]

One needs to bear in mind that pulmonary infiltrates could represent infection, inflammation or even edema. Differential diagnosis for cavitating lesions should include fungal infection and *Mycobacterium* sp.

In this particular case the patient underwent a PET/CT scan early on. The presence of a PET-positive thick-walled cavity in his right upper lobe that included a spheroid mass was highly suspicious of Aspergilloma. The radiological suspicion along with the patient's known immune deficiency made this the primary suspected diagnosis. Other viral, bacterial and fungal infections were kept in mind as well as non-infectious cases.

The appropriate investigations to more precisely diagnose the infiltrate were undertaken, including antigen titres, Galactomannan test, bronchoscopy with BAL, superdimension -bronchoscopy and transthoracic coarse needle biopsy.

With regard to suspicion of *Mycobacterium* sp., the usual tests of IGRA, PCR, microscopy and cultures were all negative. The patient also did not have the relevant exposure. Therefore, we believe that the diagnosis could be reasonably ruled out.

The patient had a negative Galactomannan antigen test and bronchoscopy cultures did not show *Aspergillus* sp. The clinical suspicion, however, was high for invasive fungal infection and treatment continued. We argue that the decision to continue treatment was appropriate since the consequence of ending treatment in a patient with invasive fungal disease could be disastrous.

It was not until the 8-month follow-up PET/CT scan showed progression in the lung infiltrate that the presumptive diagnosis of pulmonary Aspergillosis needed to be investigated further and a non-infectious inflammatory cause needed to be explored. Subsequent coarse needle biopsy revealed non-specific inflammation. No evidence of fungal infection was found.

While patients with AD HIES due to STAT3 mutation have an insufficient inflammatory response to infections, they also demonstrate exaggerated pathological inflammatory response in their lung which results in parenchymal damage. STAT3 signalling is an important inhibitor of pro-inflammatory mediators like tumour necrosis factor (TNF)α, IL-12 and IFNγ.[10] Both IL-6, which is pro-inflammatory, and IL-10, which is anti-inflammatory, signal via STAT3. STAT3 therefore regulates the inflammatory response. Decreased IL-10 and IL-21 signalling explain the elevated IgE. It is quite possible that the inflammation seen in his case was caused by such a pathological inflammatory response that caused the infiltrates.

It is likely that the initial suspicion of Aspergilloma was correct and that the progression of infiltrates was caused by subsequent bacterial infections or the exaggerated inflammatory response described above.

Finally, treatment with immunosuppressive drugs in a patient with hyper IgE syndrome is risky because patients become even more predisposed to viral, bacterial and fungal infections as well as negative effects on bone density. Patients with AD-HIES have a high incidence of osteoporosis and increased risk of bone fractures. Systemic steroid treatment further compounds this problem. No bone density scan (DEXA-scan) has been performed. This patient was treated with prophylactic Itraconazole as well as calcium with vitamin D during his Prednisolone course.

Conclusion

Patients with hyper IgE syndrome are vulnerable to pulmonary Aspergillosis due to recurrent pneumonia that causes bronchiectasis and pneumatoceles. Great care should be taken to obtain direct evidence of *Aspergillus* infection or an immunological response to *Aspergillus* sp.

Second, in patients with AD-HIES one needs to consider the possibility of non-infectious cause of pulmonary infiltrates. The infiltrates could represent inflammation or haemorrhage and therefore do not necessarily always warrant treatment for an infection.

Third, prophylactic antifungals should be strongly considered when treating patients with AD-HIES with immunosuppressive drugs due to further immune suppression in a group of patients who are already immune depressed due to their severely impaired Th17 development.

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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