

# Complicated pediatric Castleman disease treated with tocilizumab

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## Introduction

This clinical vignette presents the case of a pediatric patient with a rare form of unicentric Castleman disease (UCD) complicated by paraneoplastic pemphigus (PNP), bronchiolitis obliterans (BO) and myasthenia gravis (MG). It is important to emphasize that the patient underwent prolonged tocilizumab (anti-interleukin-6 agent) treatment, and our findings provide further data on its efficacy in treating complicated UCD.

## Case report

The patient, a 12-year-old girl, experienced her first myasthenic symptoms in July 2017.

In June 2018, she suffered from the first symptoms of pemphigus vulgaris on her oral mucosa and fingernails.

Despite treatment with intravenous immunoglobulins (IVIG), prednisone and dapsons, the changes in the mucous membranes and the nail shafts persisted, which raised the suspicion of a PNP. The patient was subsequently referred to Pediatric Oncology and Hematology for magnetic resonance imaging (MRI) of the whole body. The images revealed a pathological mass in the retroperitoneal space (approx. dimensions 40 × 30 × 130 mm) (Figure 1C). Additionally, Chromogranin A levels were significantly elevated (>700 µg/L). Post-surgical removal, a histopathological examination revealed a hyaline vascular variant, which is the most common type in pediatric Castleman disease [1

(Figure 1B). A residual mass of the tumor was noted by MRI on follow up (Figure 1A).

After presenting with mediastinal pneumothorax and two bronchial obstructions, a high-resolution computed tomography (HRCT) was performed. The imaging indicated lung involvement in the course of her pemphigus (Figure 1D). Following a consultation between the Dermatology, Pulmonology and Oncology departments, a diagnosis was made of paraneoplastic pemphigus in the course of UCD with lung involvement.

Treatment was started with rituximab, which was stopped after four doses. As no pulmonary improvement was observed, tocilizumab was then considered. MRI examination post treatment initiation with tocilizumab indicated regression of the Castleman tumor. After four doses of tocilizumab, the first sign of clinical improvement, i.e. a reduction in dyspnea, was noted.

During further treatment, the doses and weekly intervals of tocilizumab treatment were altered, depending on the clinical status of the patient to find the best treatment plan. Exact dates and doses are set out in Table I.

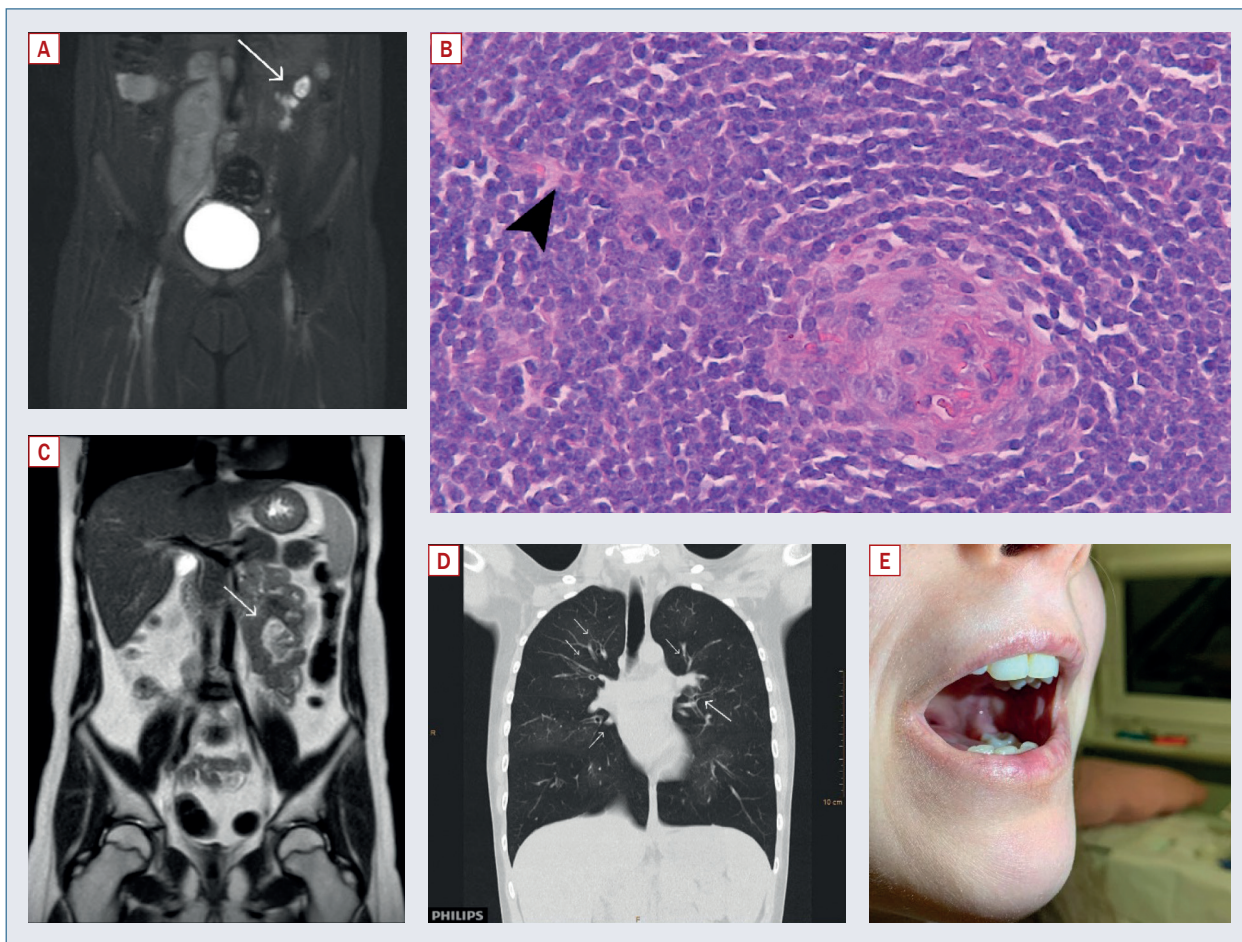
Only anemia grade 1 [hemoglobin (Hb) 10.5 g/dL] and leukopenia grade 1 [white blood cell (WBC) count 2.90 G/µL] were observed as side effects.

During the patient's last visit for a follow-up assessment, she did not report any symptoms that were related to dyspnea, and generally presented in good condition. Physical examination and auscultation of the lungs revealed an expiratory wheezing at the base of the left lung. The changes that

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Received: 28.02.2023 Accepted: 22.04.2023 Early publication date: 16.08.2023

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**Figure 1A.** Magnetic resonance imaging (MRI) showing pathological mass in retroperitoneal space; **B.** Histopathological examination revealing hyaline vascular variant; **C.** MRI after operation showing residual mass of tumor; **D.** High-resolution computed tomography scan demonstrating segmental stenosis of peripheral sections of segmental and subsegmental bronchioles; **E.** Mucocutaneous lesions of presented patient with trismus

were present in her mucous membranes, tongue and gums showed signs of redness with white plaques. Trismus was noted, as well as signs of onycholysis and scarring on her fingernails; these were attributed to fibrosis from PNP (Figure 1E).

## Discussion

In the presented case, only partial surgical resection was possible, and this may perhaps explain why symptoms did not improve after surgery.

Interleukin 6 (IL-6) is a driver of symptoms in most idiopathic multicentric Castleman disease (MCD) patients, and has been described in some inflammation-related UCD patients [2]. Some results of IL-6 levels were connected to specific timepoints; for example, the values were elevated during tocilizumab treatment (from 20 pg/mL to 75 pg/mL). Unfortunately, IL-6 was not measured at the onset of the MG or PNP symptoms. However, IL-6 was in the normal range at the UCD diagnosis but was slightly elevated after four doses of rituximab.

Nishimoto et al. [3] attributed an increase in serum IL-6 level following tocilizumab administration to the inhibition of IL-6 consumption by the IL-6 receptor; they also suggested that the IL-6 level reflects endogenous IL-6 production, and thereby indicates true disease activity.

Tocilizumab has been found to be effective in treating idiopathic MCD patients [2]; our patient's dyspnea improved after eight weeks of treatment.

Tocilizumab demonstrates acceptable tolerance; the side effects for our patient were reported to be mild.

Although patients with UCD do not demonstrate a shorter lifespan compared to the general population, PNP is a life-threatening complication and often results in progressive BO with a poor clinical outcome [4]. Although tocilizumab is not useful for preventing BO [5], it appears to have effectively stopped disease progression in our patient.

In our opinion, tocilizumab is a promising agent for treating inflammation-related symptomatic complicated UCD, even though the data regarding its efficacy is limited

Table 1. Dates and doses of immunosuppressive and immunomodulatory medications in presented patient

Date	Jun 2018	Jun 17, 2019	Jul 25, 2019	Sep 19, 2019	Oct 2019	Nov 1, 2019	May 4, 2020	Sep 25, 2020	Oct 16, 2020	Apr 9, 2021	Apr 30, 2021	Jul 23, 2021	Aug 23, 2021	Nov 23, 2021	Dec 21, 2021
Clinical manifestations	First pemphigus symptoms	Surgery	Lung involvement	Lack of pulmonary improvement	Consultation with pulmonologist			Clinical improvement							Increased frequency of dyspnea
Intravenous immunoglobulins			Immunosuppressive dose 2 g/kg every 4 weeks				Supplementary dose 0.4 g/kg acc. to IgG levels		Increase in dose 1 g/kg every 3 weeks				Supplementary dose 0.4 g/kg acc. to IgG levels		
Prednisone (per os)		Increase [1 mg/kg/d]			Decrease [0.5 mg/kg/d]										
Rituximab (i.v. infusion)			375 mg/m <sup>2</sup> every 2 weeks												
Tocilizumab (i.v. infusion)					Every 2 weeks			Every 3 weeks				Every 4 weeks			Every 3 weeks
Fluticasone & salmeterol (per inhalation)					8 mg/kg		10 mg/kg	12 mg/kg				12 mg/kg			12 mg/kg
Interleukin 6 [pg/mL]		3.4		6.2		53.8				4 at 50 µg	75.3	21			30

i.v. – intravenous

[6], and the exact dose and length of tocilizumab treatment still needs to be determined.

### Acknowledgments

The authors wish to thank Mr. Edward Lowczowski and Mr. Edward Clarke for providing language help.

### Authors' contributions

AM, SS – analysis of clinical data, literature search, data analysis, writing manuscript. JK, MG – provision of histopathological images with descriptions. DB – provision of computed tomography and magnetic resonance images. AL, JN – provision of clinical data. JT – provision of clinical data, analysis of clinical data, literature search, data analysis. All authors – critical revision and final approval.

### Conflict of interest

The authors declare no conflict of interest.

### Financial support

None.

### Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

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