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Cytokine release syndrome in non- small cell lung cancer patient receiving immune checkpoint inhibitors: A case report

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ABSTRACT

Cytokine release syndrome (CRS) is a well-described immune-related adverse event following chimeric antigen receptor T-cell therapy (CAR-T) but has rarely been reported following therapy with immune checkpoint inhibitors (ICI).

We present a clinical case of severe CRS after ICI therapy for advanced non-small-cell lung cancer (NSCLC). After the third cycle of ipilimumab and nivolumab the patient presented with fever, hypotension and somnolence, leading to acute respiratory failure, acute kidney and hepatic failure, capillary leak syndrome, requiring ICU (intensive care unit) care. She recovered after receiving tocilizumab and steroid therapy.

Subsequently, we found 17 clinical cases of advanced NSCLC patients in peer review, experiencing CRS as an adverse event of treatment with ICI. We review those cases in detail and compare the similarities and outcomes.

Conclusion: CRS is a serious, life-threatening complication that is rare after ICI therapy for solid cancers but becoming increasingly frequent since ICI therapies are broadening indications. When presented with clinical symptoms, considering CRS is crucial, as early recognition is key to timely intervention and favorable outcome for the patient.

1. Introduction

Immune checkpoint inhibitor therapy has revolutionized the treatment of NSCLC[1], leading to improved overall survival in both first- and next-line settings in advanced stage disease. (Mok et al., 2019) Despite their effectiveness, these treatments are linked to a range of immune-related adverse events (IRAEs).

CRS[2] is a potentially life-threatening systemic inflammatory response that has mostly been associated with chimeric antigen receptor T-cell (CAR-T) therapy and with natural and bispecific antibodies. (Lee et al., 2014; Zhang et al., 2024) Although rarely (described only in case reports), CRS has also been mentioned as a possible adverse event of treatment with ICI[3]. (Sackstein et al., 2021; Heynemann et al., 2024; Yomota et al., 2021; Tsutsui et al., 2023; Honjo et al., 2019; Normand et al., 2021; Sumi et al., 2022; Tanaka et al., 2024; Murata et al., 2022; Deng et al., 2022; Kunimasa et al., 2021 Dec 31; M Zhang et al., 2022; Xinyu PhDa Zhang et al., 2022; Kogure et al., 2019; Nakashima et al., 2023; Rassy et al., 2017; Zhang et al., 2024) The incidence is estimated to be about 0.07 %. (Zhang et al., 2024)

CRS, associated with ICIs, occurs due to the over activation of the immune system. ICIs, such as anti-CTLA-4[4] (e.g. ipilimumab), anti-PD-1[5] (e.g. pembrolizumab), and anti-PD-L1[6] antibodies (e.g. atezolizumab, durvalumab), work by blocking inhibitory pathways that regulate the immune response, leading to enhanced T-cell activity against tumors (Nirschl and Drake, 2013). However, this immune activation can become excessive, resulting in the widespread release of inflammatory cytokines like IL-6, IFNγ, and TNFα (Johnson et al., 2018). This hyper activation can cause systemic inflammation, endothelial damage, and multi-organ dysfunction.

CRS symptoms can vary greatly and are often very similar to those of an infection. There are several grading systems that divide CRS into different subgroups, according to severity of symptoms (grading system is explained in the Section 2.2.1). The main indicator is fever, but it can escalate to hypotension and respiratory distress, requiring careful monitoring and management since it can lead to multi organ failure and death (Michot et al., 2016). Considering this, it is essential to first rule

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out the possibility of infection, empiric antibiotic therapy should be initiated after collecting appropriate cultures. (Lee et al., 2014)

Case reports have demonstrated that immunosuppression using tocilizumab, an anti-IL-6 receptor antibody, with or without corticosteroids, to be effective in this setting, if used in a timely manner. (Lee et al., 2014; Sackstein et al., 2021; Heynemann et al., 2024; Yomota et al., 2021; Kunimasa et al., 2021 Dec 31)

With increased use of ICI, which are expanding their indications, we can expect the number of reported cases to rise as well.

Here, we present a clinical case of CRS in a patient receiving ICI for the treatment of advanced NSCLC, followed by a brief review of 18 similar clinical cases. We emphasize the importance of recognizing the possibility of CRS as a rare, but life-threatening complication of ICI treatment and highlight the importance of timely and appropriate management.

2. Cases and methods

2.1. Case report

We present a case of a 62-year-old female patient, smoker, otherwise healthy, with no chronic comorbidities or therapy. Until recently, she was physically active, with only a history of cholangitis and pancreatitis. During routine check-ups, incidentally at least 6 bilateral lung lesions in both lower lobes identified, the largest being 40 mm (Fig. 1). CT scans of the abdomen and head did not show any distant metastases. Clinical stage of disease was cT2bN0M1a. Histologically it was a mucinous adenocarcinoma with KRAS, p.G12V gene mutation on the NGS 77 gene panel testing (Oncomine Precision Assay ThermoFisher®), PD-L1 status 0 %. In August 2023, she started treatment with a combination of chemotherapy and immunotherapy consisted of ipilimumab at 1 mg/kg every six weeks plus nivolumab at 360 mg every 3 weeks combined with chemotherapy every 3 weeks for two cycles, consisted of carboplatin area under curve (AUC) = 5 plus pemetrexed at 500 mg/m^2. The first two cycles ensued without major complications, noting only hyperthyroidism, which did not require specific therapy.

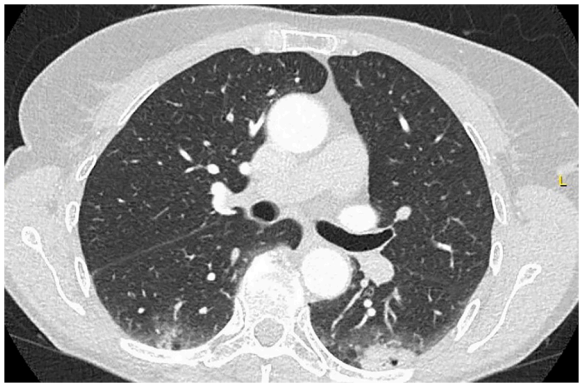

Fig. 1. CT scan of thorax. Source: University Clinic Golnik.

After the third cycle, when only ipilimumab and nivolumab were administered, she presented at the local emergency department 14 days later due to several days of extreme fatigue, weakness, followed by vomiting and fever up to 39 °C. On examination, she was hypotensive, tachypneic, and somnolent. Bilateral inguinal and perineal rash, appearing 5 days earlier, was described. Microbiological samples were collected (but remained negative) and empirical broad spectrum antibiotic therapy with ceftriaxone and flucloxacillin was initiated. Abundant hydration and oxygen supplementation were administered. Abdominal ultrasound revealed no possible focus of infection. Echocardiography showed normal ejection function without valvulopathies, indicating signs of hyperdynamic circulation. Hemocultures remained negative, as well as serology for hepatitis B, C and HIV (human immunodeficiency virus). A skin biopsy of the rash was performed, excluding DRESS (drug reaction with eosinophilia and systemic symptoms).

Due to persistent deterioration, she was transferred to the ICU[7], oxygen requirement increased to high-flow oxygen therapy (flow rate 40 L/min, FiO2 100 %), she needed vasoactive support with norepinephrine, followed by vasopressin, and albumin replacement. Laboratory findings showed elevated inflammatory parameters (CRP 320 mg/L [<5 mg/L], PCT 38.8 μg/L [<0.5 μg/L], WBC 15.4 × 10^9/L [4.00–10.00 × 10^9/L]), cortisol 1200 nmol/L[172–497 nmol/L], IL-6 108.878 pg/ml [<3.4 pg/mL]), worsening renal function with a creatinine value of 234 μmol/L. First, therapy with methylprednisolone (100 mg SoluMedrol i.v.) and SLEDD (Sustained Low Efficiency Dialysis) with CytoSorb (a single-use device containing adsorbent polymer beads designed to remove cytokines, as blood passes through the device) was introduced without improvement. Due to suspected CRS, she received tocilizumab at a dose of 600 mg. Shortly after administration, the need for vasopressor support and oxygen supplementation significantly decreased and could be discontinued completely 48 h afterwards.

Laboratory findings showed rapid decline of CRP and IL-6 levels as shown in Figs. 2 and 3. The kidney and liver function gradually restored.

D1-D16: days of hospitalization when laboratory parameters were measured (D1: day of submission to the hospital; D2: day of tocilizumab administration).

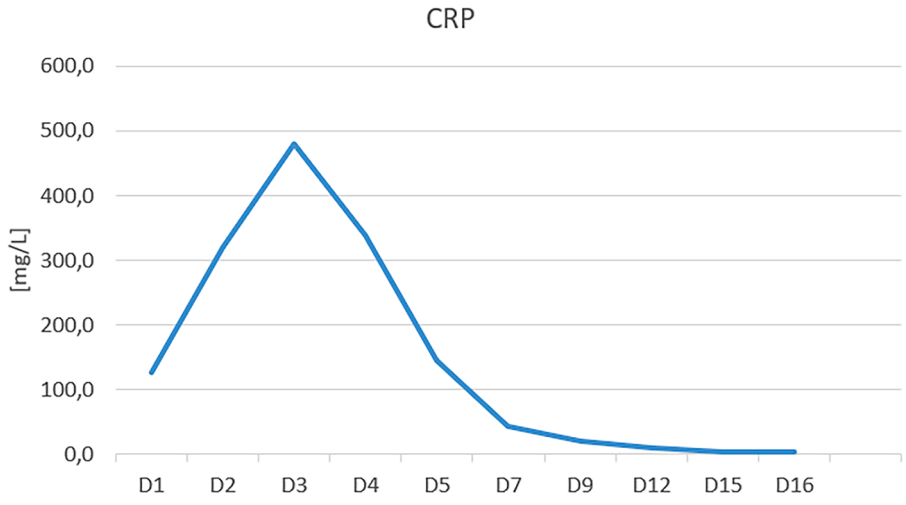

Fig. 2. Rapid decline of CRP (C-reactive-protein) values after tocilizumab administration.

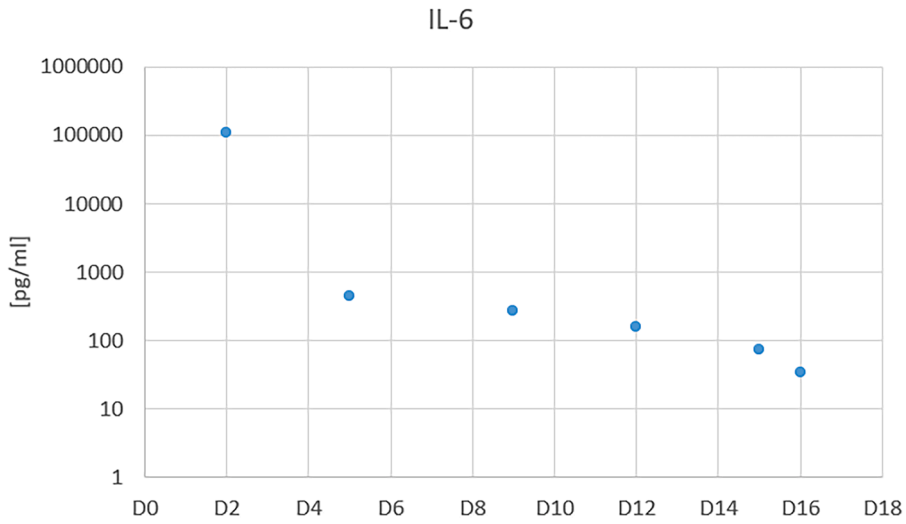

Fig. 3. Rapid decline of IL-6 (interleukin-6) values after tocilizumab administration.

D1-D16: days of hospitalization when laboratory parameters were measured (D1: day of submission to the hospital; D2: day of tocilizumab administration)

Eventually, after 23 days of hospitalization (10 days in the ICU), she was discharged with gradual tapering of corticosteroids over the next 6 weeks. Afterwards she needed hydrocortisone supplementation, due to adrenal gland insufficiency. Upon progressive disease, a broader spectrum NGS testing was performed, consisting of 229 gene signature, resulting in mucinous adenocarcinoma with KRAS, p. G12V mutation, ARID1A, p.Ser686ProfaTer56 point mutation and SMAD4, p.Glu526Ter mutation (Oncomine Precision Assay ThermoFisher®). The molecular tumor board suggested treatment with a different chemo-immunotherapy approach, consisting of carboplatin, pemetrexed and pembrolizumab, which she received without a further episode of CRS or another immune related adverse event.

2.2. Case series of 18 patients and literature review

Subsequently, we found 17 clinical cases, published in peer reviewed medical journals, involving lung cancer patients experiencing CRS as an adverse event of treatment with ICI.

The majority of included patients were male (67 %), with a median age of 61.5 years, being diagnosed with NSCLC (89 %) in the metastatic stage (67 %). On average, they received 4 cycles of ICI treatment prior to an adverse event, one-third-of CRS cases happening after the first ICI cycle. Ten patients (56 %) were receiving a PD-1 inhibitor (pembrolizumab/nivolumab/sintilimab), 6 patients (33 %) a combination of PD-1 and CTLA-4 inhibitor (nivolumab+ipilimumab), and 2 patients (11 %) PD-L1 inhibitor (atezolizumab) (Table 1). Seven patients received a combination of chemotherapy with ICI (immune checkpoint inhibitors).

2.2.1. CRS severity and treatment

The severity of CRS was graded according to the scale proposed by Lee at al. Grade 1 severity refers to symptoms that are not life threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise. Grade 2 includes symptoms that require and respond to moderate intervention (oxygen requirement <40 % FiO2 or hypotension responsive to i.v. fluids or low dose of one vasopressor or G2 organ toxicity. Grade 3 includes symptoms that require and respond to aggressive intervention (oxygen requirement ≥40 % FiO2 or hypotension requiring high-dose or multiple vasopressors or G 3 organ toxicity or G4 transaminitis). Grade 4 refers to life-threatening symptoms which require ventilator support or G4 organ toxicity (excluding transaminitis). (Lee et al., 2014)

Table 1
Characteristics of patients, suffering from CRS, followed by ICIs. Anti-PD-1, anti-Programmed Death-1; anti-PD-L1, anti-Programmed Death-Ligand-1; anti-CTLA-4, anti-Cytotoxic T-Lymphocyte Antigen 4.

Characteristics	Patients (n = 18)
Median age (lower and upper range)	61.5 (36–79)
Gender	
• Male	12 (67 %)
• Female	6 (33 %)
Cancer stage	
• II-III	6 (33 %)
• IV	12 (67 %)
Cancer type	
• NSCLC	16 (89 %)
• Pleomorphic LC	2 (11 %)
PD-L1 status	
• Positive	9 (50 %)
• 0 %	3 (17 %)
• No data	6 (33 %)
Median No of cycles (lower and upper range)	4.2 (Mok et al., 2019; Lee et al., 2014; Johnson et al., 2018; Nirschl and Drake, 2013; Michot et al., 2016; Sackstein et al., 2021; Heynemann et al., 2024; Yomota et al., 2021; Tsutsui et al., 2023; Honjo et al., 2019; Normand et al., 2021; Sumi et al., 2022)
• After 1st cycle	6 (33 %)
Type of ICI used	
• Anti-PD-1	10 (56 %)
• Anti-PD-L1	2 (11 %)
• Anti-CTLA-4/anti-PD-1	6 (33 %)

Eight patients (44.4 %) suffered a G1 or G2 reaction, 7 patients (38.9 %) had a G3 or G4 reaction and 3 patients (16.7 %) died as a consequence of CRS. More data in Fig. 4. All 7 patients who received concomitant chemotherapy suffered from at least G3 reaction (2 patients G3, 3 patients G4 and 3patients G5 reaction).

All patients with available data (12/18) showed elevated inflammatory parameters (CRP and IL-6 values) and all patients received prophylactic antibiotic therapy and corticosteroids. Five patients with at least G3 severity of CRS subsequently received therapy with tocilizumab. In three patients, the condition rapidly improved after receiving one dose of tocilizumab, while two required re-administration of another dose.

Another two patients that experienced at least G3 AE[8], received other cytokine-targeted therapies (TNF-alpha inhibitor and IL-1 inhibitor), while for the three patients with G5 CRS, tocilizumab or other immunosuppressive therapy was either unavailable or it was not considered.

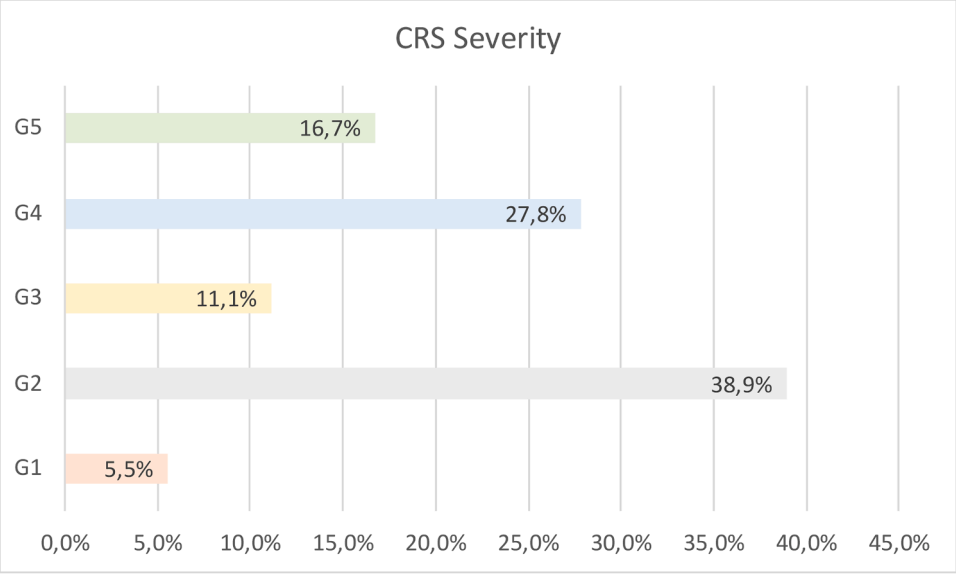

Fig. 4. CRS severity. Percentage of patients, suffering from G1-G5 CRS. G (Mok et al., 2019; Lee et al., 2014; Johnson et al., 2018; Nirschl and Drake, 2013; Michot et al., 2016): grade of adverse event (CRS).

The calculated average duration of hospitalization or treatment with corticosteroids regarding CRS was 5.5 weeks (excluding 4 patients who suffered from G5 and 1 patient for whom no data was available).

Only three patients (16.7 %) were rechallenged with ICI therapy, two of them previously experiencing G1 and G2 AE and one experiencing G4 AE. Additional two patients were considered to continue ICI therapy, but they refused.

The majority of patients (77.5 %) achieved disease control after ICI therapy, one (5.5 %) complete response, 8 (44 %) partial response and 5 (28 %) stable disease. Progressive disease was described in only three patients (17 %). Disease response rate was evaluated by RECIST 1.1 criteria. Data were not available for 1 patient (5.5 %) (Fig. 5). However, tumor response did not correlate with the severity of the CRS. (Sackstein et al., 2021; Heynemann et al., 2024; Yomota et al., 2021; Tsutsui et al., 2023; Honjo et al., 2019; Normand et al., 2021; Sumi et al., 2022; Tanaka et al., 2024; Murata et al., 2022; Deng et al., 2022; Kunimasa et al., 2021 Dec 31; M Zhang et al., 2022; Xinyu PhDa Zhang et al., 2022; Kogure et al., 2019; Nakashima et al., 2023; Rassy et al., 2017; Zhang et al., 2024)

3. Discussion

Cytokine Release Syndrome (CRS) is a well-documented immune-related adverse event that can lead to life-threatening complications. Although it is more commonly associated with chimeric antigen receptor T-cell (CAR-T) therapy, CRS has been reported following treatment with ICIs. CRS can manifest with severe symptoms such as fever, hypotension, respiratory distress, and multi-organ failure, which can be fatal if not promptly treated.

With a limited number of case reports and lack of data about CRS in pivotal clinical trials with ICI agents for the treatment of metastatic NSCLC, there is no established diagnostic criteria or treatment guidelines. (Zhang et al., 2024) The initial treatment for patients with mild to moderate symptoms involves administering intravenous

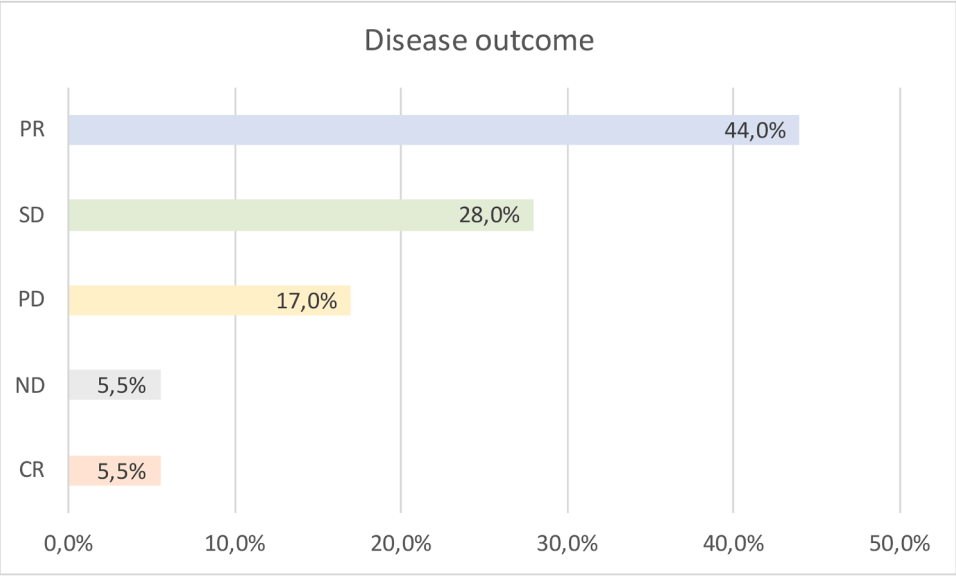

Fig. 5. Disease outcome after ICI therapy. PR, partial response; SD, stable disease; PD, progression disease; CR, complete response; ND, no data.

methylprednisolone (mPSL). In severe cases, which need ICU admission, various cytokine antagonists are being considered additionally as potential treatment options. Tocilizumab, anti-IL-6 agent, is advised for all patients with CRS exceeding G2 CRS, and for patients with G1 CRS with comorbidities or elderly. (Lee et al., 2014) Both our case and others, showed significant improvement after receiving tocilizumab when presented with severe CRS, highlighting the efficacy of this treatment approach (Sackstein et al., 2021; Heynemann et al., 2024; Yomota et al., 2021; Kunimasa et al., 2021 Dec 31), which generates a question whether it should be used earlier in the process.

Upon reviewing all case series, we discovered that all of the 7 patients who received concurrent chemotherapy experienced CRS of at least grade 3 or more, suggesting that concurrent treatment with chemotherapy could potentially increase the likelihood of a more severe course of CRS. However, a larger patient sample would be needed to confirm this hypothesis.

Regarding further treatment and outcomes, most patients who experienced CRS did not receive subsequent ICI therapy due to the fear of severe immune related adverse event recurrence. (Yomota et al., 2021; Normand et al., 2021; M Zhang et al., 2022; Zhang et al., 2024) However, in three patients who were rechallenged with ICIs, CRS did not reappear, suggesting that with careful monitoring, reintroduction of ICIs may be possible in selected cases. (19, 21) This indicates that while CRS is a serious concern, it does not necessarily preclude future ICI therapy in patients.

3.1. Conclusion

Given the potential severity of CRS, it is crucial to consider alternative approaches to managing this syndrome. Early recognition of CRS symptoms and swift intervention are vital. Clinicians should maintain a high index of suspicion for CRS in patients receiving ICIs and promptly perform laboratory diagnostics, including measuring cytokine levels such as IL-6. Initiating treatment with anti-IL-6 agent at the first signs of CRS can significantly improve patient outcomes. (Lee et al., 2014; Sackstein et al., 2021; Heynemann et al., 2024; Yomota et al., 2021; Kunimasa et al., 2021 Dec 31) By incorporating these strategies, we can enhance the management of CRS and improve the safety and efficacy of ICI therapy for patients with advanced solid cancers.

Abbreviations

Non-small-cell lung cancer
Cytokine release syndrome
Immune checkpoint inhibitor
Anti-cytotoxic T-lymphocyte antigen 4
Anti-programmed death-1
Anti-programmed death ligand-1
Intensive care unit
Adverse events

Patient consent statement

The authors declare that they have obtained consent from the patient.

CRediT authorship contribution statement

Ana Geltar: Conceptualization, Data curation, Investigation, Visualization, Writing – original draft. **Assist Urska Janzic:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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