

Infliximab attenuates paediatric inflammatory multisystem syndrome in SARS-CoV-2 (PIMS-TS).

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Short title: PIMS-TS attenuated by Infliximab

Table of contents summary: PIMS-TS presentation and course may be attenuated by established infliximab therapy and such medications are potentially key in treating this novel condition.

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Abbreviations:

Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. (PIMS-TS); Multisystem inflammatory syndrome in children (MIS-C); Coronavirus disease 2019 (COVID-19); anti-Tumor Necrosis Factor-alpha (anti-TNF- α); C-reactive protein(CRP); erythrocyte sedimentation rate (ESR); lactate dehydrogenase (LDH); pyrexia of unknown origin (PUO); intravenous immunoglobulin (IVIG); Polymerase chain reaction (PCR); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS); inflammatory bowel disease (IBD); Ulcerative colitis (UC), Paediatric Ulcerative Colitis Activity (PUCAI); intravenous (IV); Royal College of Paediatrics and Child Health (RCPCH); Center for Disease Control (CDC); World Health Organization (WHO); ribonucleic acid (RNA); extracorporeal membrane oxygenation (ECMO); human anti-mouse antibodies (HAMA); anti-drug antibodies (ADA).

Contributors' Statement Page:

Dr Joseph Meredith, Dr Paul Henderson, Prof David C. Wilson, Prof Richard K. Russell conceptualised and designed the case report, drafted the initial manuscript, reviewed and revised the manuscript.

Cher-Antonia Khedim, Bachelor of Nursing (BN), Master of Science (MSc), contributed significantly to the care of the patient.

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The patient and family are aware of the writing of this manuscript and have provided written consent for its publication.

Abstract

Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) is a newly described condition. It has a spectrum of presentations related to hyperinflammation and cytokine storm. We report the first case of PIMS-TS in a child on established anti-Tumor Necrosis Factor-alpha (anti-TNF- α) therapy; a 10 year-old girl with ulcerative colitis treated with infliximab. The patient had 6-weeks of daily fever with mucocutaneous, gastrointestinal, renal and hematologic involvement. Biomarkers of hyperinflammation were present including: hyperferritinaemia (up to 691 μ L; normal 15-80 μ g/L), C-reactive protein (CRP) (>100mg/L for >10 days, normal 0-5 mg/L), erythrocyte sedimentation rate (ESR) consistently >100mm/hr (normal 0-15 mm/hr), raised white cell count with neutrophilia, elevated D-dimer and lactate dehydrogenase (LDH), anaemia and Mott cells on bone marrow analysis.

Extensive investigations for alternative diagnoses for pyrexia of unknown origin (PUO) were negative. The condition was refractory to treatment with intravenous immunoglobulin (IVIG) but improved within 24hrs of high dose methylprednisolone. Infliximab treatment followed and the patient has remained well at follow up. Polymerase chain reaction (PCR) and serology for SARS-CoV-2 were negative. Current series report such negative findings in up to half of cases. The patient experienced a milder clinical phenotype without cardiac involvement, shock or organ failure. It is postulated that prior anti-TNF- α therapy attenuated the disease course. Infliximab therapy may interfere with serology testing and produce false negative results. This case supports the need for investigation into infliximab as primary therapy for PIMS-TS.

What is known on the topic?

- 1) Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), also referred to as multisystem inflammatory syndrome in children (MIS-C) temporally related to Coronavirus disease 2019 (COVID-19), is a newly described clinically entity occurring approximately 2-4 weeks post infection.
- 2) PIMS-TS clinical presentations fall within a spectrum from severe cardiac dysfunction, toxic shock-like syndrome to features indicative of Kawasaki's disease or multisystem hyperinflammation with hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) features in some.
- 3) Most cases are severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) negative but serological evidence of previous infection is present in at least half of cases. This, along with temporality and laboratory data, supports the hypothesised post-infectious, immune-mediated nature of the condition.
- 4) There is no current consensus on optimal therapy. High dose intravenous corticosteroids and IVIG, either alone or in combination, have been used in most cases. Many have required cardiac and circulatory support. Occasional use of biological therapies, including anti-Tumor Necrosis Factor-alpha (anti-TNF- α) drugs, has also been reported.

What new information does this case contribute?

- 1) The PIMS-TS disease presentation and course of illness may be significantly attenuated in the context of established treatment with anti-TNF- α drugs, such as infliximab.
- 2) Paediatric patients being treated with anti-TNF- α therapies who present with persistent, non-specific features of hyperinflammation – such as pyrexia of unknown origin (PUO) – should have PIMS-TS considered as part of the differential diagnosis and investigated accordingly.
- 3) Diagnosis of the condition via serology may be complicated by monoclonal antibody therapy such as infliximab.
- 4) Anti-TNF- α drugs such as infliximab have potential as primary therapy in the management of PIMS-TS.

Introduction

Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), also referred to as multisystem inflammatory syndrome in children (MIS-C) temporally related to Coronavirus Disease 2019 (COVID-19), is a newly reported clinical entity.¹ It is currently understood as a post-infectious, hyperinflammatory, immune-mediated syndrome typically following 2-4 weeks after infection with SARS-CoV-2. It represents a spectrum of disease with overlapping features of toxic shock syndrome, atypical Kawasaki's disease and multisystemic inflammation. While the antecedent infection is frequently mild, patients subsequently present with recurrent fever and symptoms associated with inflammation in one or more organs. Biochemical features of hyperinflammation are present and may resemble an hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) picture. Cardiac and/or multiorgan dysfunction predominate in many.²⁻⁸

We report the first case of PIMS-TS in a child on maintenance anti-TNF- α therapy and postulate that this therapy attenuated the clinical phenotype.

Case Report

A 10yr old female experienced 6 weeks of daily fever exceeding 38.5°C having been an inpatient at our regional center from week 3 with previous local hospitalisation. Associated symptoms included rigors, chills, diaphoresis, severe lethargy and oromucosal, aphthous, ulcers. There was bloody diarrhoea and abdominal pain in week 2 of the illness. She also reported dysguesia. Weight loss of 6kg (10% premorbid body weight) was documented over the course. She had bilateral cervical and submandibular lymphadenopathy without respiratory symptoms, rash or other symptoms.

She had been diagnosed 2 years previously with ulcerative colitis (UC) and was treated with infliximab 10mg/kg 6-weekly and oral mesalazine 2 grams daily. The most recent infliximab

dose was 6 weeks before illness onset with a therapeutic trough level of 6.7mg/L (range 2-8 µg/mL). No anti-drug antibodies were detected. Her UC was in clinical and biochemical remission prior to presentation (faecal calprotectin 37µg/g four months prior; normal <50 µg/g).

Family history was significant in terms of mixed racial ethnic background (Polynesian/Caucasian) and a parent with IBD. Weight for age was on the 100th centile (z-score 2.8), BMI 97th centile (z-score 1.84) based on World Health Organization (WHO) parameters.⁹ A sibling had been unwell with a respiratory illness. Respiratory and cardiac examinations were normal, there was no organomegaly or concerning lymphadenopathy, nor other features indicative of Kawasaki's disease. Ophthalmology, joint, perianal and external genitalia examinations were normal. The Paediatric Ulcerative Colitis Activity (PUCAI) score did not exceed 20 throughout the admission.¹⁰ Faecal calprotectin on presentation was 1020ug/g. Key laboratory values are listed in **Table 1**.

Of note is the elevated white cell count with neutrophil predominance, elevated C-reactive protein (CRP)(> 100mg/L for > 10 days), hyperferritinaemia, elevated ESR and hypoalbuminemia. There was no hypertriglyceridaemia or hypofibrinogenaemia.

Lymphocyte count mostly resided in the low normal range. T cell subsets were normal and IgG levels were raised. D-dimer was elevated at 750ng/mL (normal 0-200ng/mL). Repeated troponin I levels were not elevated. There was evidence of stage 1 acute kidney injury in week 6 and proteinuria was present (urine protein/creatinine ratio 30-108mg/mmol [normal <15mg/mmol]).¹¹ Vitamin D level was insufficient (Vitamin D3 level 42nmol/L, normal >50nmol/L) and she was Epstein-Barr virus and cytomegalovirus naïve.

Extensive infectious disease and immunological investigations were negative. Several SARS-CoV-2 PCR throat swabs over the admission were negative as was stool SARS-CoV-2 P

testing on admission. SARS-CoV-2 IgG in week 5 of illness and post discharge (week 10) were negative (Abbott Architect Immunoassay).¹² Chest Xray, whole body magnetic resonance imaging, pelvic and abdominal ultrasounds showed no clinically significant abnormality. Serial transthoracic echocardiograms and electrocardiograms were normal. Bone marrow analysis revealed an elevated plasma/lymphocyte count ratio with Mott cells, indicative of immune dysregulation or lymphoproliferation, and known to be a by-product of marked antigenic stimulus.^{13,14} There was no evidence for malignancy or haemophagocytosis. Seven days of IV piperillin/tazobactam, followed by five days of IV meropenem early in the presentation had little impact on clinical or biochemical parameters.

Following rheumatological and immunological consultation she received 2 grams of intravenous immunoglobulin (IVIG). Given no appreciable clinical response and significant headache afterwards, this was followed by a course of high dose intravenous methylprednisolone (1gram daily for 3 consecutive days). High dose aspirin (10mg/kg/oral/four times daily), proton pump inhibition and adjuvant thromboprophylaxis measures were initiated. Fevers ceased within <24hrs from the first steroid dose. The CRP level declined ten-fold within 24hrs (110 to 12mg/L) and ferritin halved over several days. The patient was discharged with a rapid weaning course of oral prednisolone, low dose aspirin and was administered a 10mg/kg intravenous infusion of infliximab in the following week. The patient remains well at follow up 4 weeks post discharge.

Discussion

We report the first case of PIMS-TS (SARS-CoV2 PCR and serology negative) in a patient receiving maintenance anti-TNF- α therapy. The attenuated clinical phenotype in this context

adds weight to the hypothesised immune-mediated, cytokine-driven pathobiology. It dictates further consideration for such agents as key therapeutics.

PIMS-TS has emerged as a novel clinical entity from April 2020 with approximately 300 reported cases to end of May, 2020.^{5,15,16} Negative PCR testing and evidence of serological conversion in many supports the current understanding of a post-infectious, immune-mediated condition. Case definition from the Royal College of Paediatrics and Child Health (RCPCH) and the Center for Disease Control (CDC) does not necessitate PCR or serological confirmation.^{1,5} The largest case series to date, from Public Health France, reports evidence of PCR or serological conversion in 86 of 172 cases (50%). Interestingly, cases without myocarditis, as in our case, were far more likely to lack PCR or serological evidence.¹⁷ Unpublished data from London reports 19 of 37 (51%) cases with IgG positive results and 23 of 37 (62%) with PCR and/or IgG confirmation of SARS-CoV-2.⁵ Verdoni's smaller Italian series reports 20% negative serology rates and 20% positive on PCR testing.¹⁸

Despite evidence for faecal shedding of SARS-CoV in the stool for up to 30 days faecal PCR testing was negative in our patient.¹⁹ Significant gastrointestinal symptoms and inflammation have been reported with COVID-19 and PIMS-TS and this was a probable cause for the raised faecal calprotectin despite only mild PUCAI score on admission.^{1,20,21} Calprotectin has been shown to be a biomarker of gastrointestinal inflammation in COVID-19 without correlating with faecal ribonucleic acid (RNA) levels.²² Multiple infection screens were negative and the clinical picture was not in keeping with an ulcerative colitis flare.

Case series from the UK, USA, Italy and France report high rates of intensive care admissions for circulatory support.^{2,17} Verdoni described a 30-fold rise in the incidence of Kawasaki's disease in April in Bergamo province with a series of 10 children in whom 60% had significant cardiac involvement and half had features of shock or MAS.¹⁸ Belhadjen described 35 cases who required intensive support, including a third with extracorporeal membrane oxygenation (ECMO) requirements.⁶ Similar data is emerging from the USA, with over 100 cases documented from New York State alone.^{5,8,16} Most children have responded well to the different treatment regimens applied. At least five fatalities in PIMS-TS have been reported to date.¹⁵

While our patient clearly met the case definition for PIMS-TS (recurrent fever, hyperinflammatory biomarkers with mucocutaneous, gastrointestinal, renal and haematologic involvement) her clinical phenotype was far less severe. We hypothesise that her maintenance anti-TNF- α therapy modified her disease course with consistently therapeutic infliximab levels. Infliximab has a terminal half-life approximating ten days (on 5mg/kg dose) with prolonged bioavailability, accumulation on repeated dosing and slow clearance rates so would still have been present at the time of presentation.^{23,24}

In addition to potentially modifying the disease presentation and course, infliximab also potentially interferes with serological testing for the condition. A caveat from manufacturers of serology testing available at our institution is to interpret with caution in patients receiving treatment with preparations involving mouse monoclonal antibodies.¹² There is potential interference from human anti-mouse antibodies (HAMA) producing false negatives in assay kits using mouse monoclonal antibodies due to blockade of binding of the diagnostic

antibody plus other possible mechanisms. False positive results may also occur.²⁵ Some manufacturers report using HAMA blockers to reduce such interference but further studies are required to identify the impact of HAMA's in serology testing in the current pandemic.²⁶ HAMA's may be distinct from anti-drug antibodies (ADA) which had not been detected previously in our patient.²⁷ It is important to be aware of this caveat and it may in part explain the negative serology in this case.

There is no currently established consensus on management of PIMS-TS. IVIG, high dose corticosteroids and less frequently biologicals have been used in a variety of combinations with varying success.^{2,5,6,8,18} Of note, infliximab is used successfully to treat the related condition of Kawasaki's disease.²⁸ Aspirin and heparin-based products have been administered for anti-inflammatory purposes and in view of concerns around increased thromboembolic risk.^{1,29}

Evidence supporting the role of TNF- α in this syndrome comes from a recent case report from Dolinger and colleagues who showed rapid clinical improvement in a patient with PIMS-TS, receiving primary infliximab treatment in the context of co-presentation with newly diagnosed Crohn's disease.³⁰ Concerns around adverse outcomes associated with anti-TNF- α treatment and COVID-19 are not supported by current evidence.^{31,32} Evidence implicating a key role of TNF- α in the immune mediated sequelae of COVID-19 are accumulating.^{29,33,34}

In summary, this first reported case of PIMS-TS in a patient on maintenance anti-TNF- α therapy provides several key insights. The presentation of disease may be attenuated so requires a high index of suspicion. Serologic testing may be negative in up to half of PIMS-TS cases, especially in those without myocarditis, so clinical diagnosis is key. Serological assays may be affected by treatment with monoclonal antibodies such as infliximab. Finally, anti-TNF- α therapies warrant further investigation in the primary management of this condition.

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Table 1 – Laboratory results summary after hospitalisation on day 16 of fever with relevant maximum or minimum values.

		Result	Reference	On day*
Hb	(min)	65	115-155 g/L	37
Platelet	(min)	323	150-400 $\times 10^9$ /L	33
White cell	(max)	23.7	4.5-14.5 $\times 10^9$ /L	42
Neutrophil	(max)	18	1.5-8 $\times 10^9$ /L	18
Lymphocyte	(min)	0.5	1.5-7 $\times 10^9$ /L	30
CRP	(max)	206	0-5 mg/L	19
ESR	(max)	>130	mm/hr	29-36
Ferritin	(max)	691	15-80 μ g/L	37
D-dimer	(max)	765	0-230 ng/ml	33
Fibrinogen	(min)	2.9	1.5-4 g/L	45
Troponin I	(max)	<1	1.0-26.0 ng/L	35
LDH	(max)	410	125-220 U/L	38
IgG	(max)	22	5-16 g/L	25

*Day of fever

		Result	Reference	On day
Sodium	(min)	136	132-144 mmol/L	21
Creatinine	(max)	86	26-57 μ mol/L	30
Albumin	(min)	22	28-45 g/L	41
Urine prot/creat	(max)	108	<15 mg/mmol	26
ALT	(max)	53	0-50 U/L	44
Amylase	(max)	86	24-110 U/L	36
Vit D3		42	>50 nmol/l	50
Infliximab level		6.7	2-8 μ g/mL	6wks prior
Anti-drug antibodies		nil		6wks prior
Faecal calprotectin		1020	<200 μ g/g	14
SARS-CoV-2 IgG		Negative		36
SARS-CoV-2 PCR (throat)		Negative		10, 15, 18, 29
SARS-CoV-2 PCR (faeces)		Negative		13, 14
Bone marrow		Elevated plasma/lymphocyte count ratio with Mott cells		