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Paediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in a patient receiving Infliximab therapy for Inflammatory Bowel Disease.

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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).

Author Contributions:

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 substantially in conception of the manuscript, data acquisition, drafting and revision. All authors approved the final manuscript and agree to be accountable for all aspects of the work.

Patient Anonymity and Informed consent:

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 proposed to occur as part of a post-infectious immune response. 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 µg/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. Accepting the wide spectrum of PIMS-TS presentations, it is possible that prior anti-TNF-α therapy may have attenuated the disease course. Given the uncertainty around therapeutic strategies for PIMS-TS this case supports the need for further investigation into continuing infliximab as a treatment option for the condition.

1. Introduction

Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), also referred to as multisystem inflammatory syndrome in children (MIS-C), is a newly reported clinical entity.[1] It is currently understood as a post-infectious, hyperinflammatory, immune-mediated syndrome following 2-4 weeks after infection with SARS-CoV-2. It represents a spectrum of disease with overlapping features of toxic shock syndrome, 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. Gastrointestinal symptoms are present in approximately three out of every four patients, whereas respiratory symptoms are infrequent (<5%). Cardiac and/or multiorgan dysfunction predominate in many.[2-9]

We report the first case of PIMS-TS (SARS-CoV2 PCR and serology negative) in a child on maintenance anti-TNF-α therapy.

2. Case Report

A 10yr old female experienced 6 weeks of daily fever exceeding 38.5°C having been an inpatient at our center from week 3 with previous local hospitalisation. Associated symptoms included rigors, chills, diaphoresis, dysgeusia, severe lethargy and oromucosal, aphthous, ulcers. There was bloody diarrhoea and abdominal pain in week 2. Weight loss of 6kg (10% body weight) was documented. 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).[10] A sibling had been unwell with a respiratory illness in the weeks preceding presentation, however no SARS-CoV-2 testing was performed due to lack of availability at that time and the mild nature of the illness. Respiratory and cardiac examinations were normal, there was no organomegaly, concerning lymphadenopathy, nor other features 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.[11] Faecal calprotectin on presentation was 1020ug/g. Key laboratory values are listed in **Table 1**.

Of note is the elevated white cell count with neutrophilia, 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. Troponin I levels were normal. There was stage 1 acute kidney injury in week 6 with proteinuria (urine protein/creatinine ratio 30-108mg/mmol [normal <15mg/mmol]).[12] Vitamin D level was insufficient (42nmol/L, normal >50nmol/L) and she was Epstein-Barr virus and cytomegalovirus naïve.

Extensive and repeated infectious disease, rheumatologic and immunological investigations for an extremely broad differential diagnosis were negative. (Refer to notation for Table 1.) Several SARS-CoV-2 PCR throat swabs over the admission were negative as was stool SARS-CoV-2 PCR on admission. SARS-CoV-2 IgG in week 5 of illness and post discharge (week 10) were negative (Abbott Architect Immunoassay).[13] 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 and marked antigenic stimulus and increasingly recognised on blood films post SARS-CoV-2 .[14,15]There was no evidence for malignancy or haemophagocytosis. Seven days of IV pipercillin/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 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 were also 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 8 weeks post discharge.

3. Discussion

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

PIMS-TS has emerged as a novel clinical entity from April 2020 with at least 800 reported cases to June, 2020. [2,16-18] . Case definition from the Royal College of Paediatrics and Child Health (RCPCH) does not necessitate PCR or serological confirmation, but the WHO (World Health Organization) and Center for Disease Control (CDC) require prior contact with an individual with COVID-19. [1,4,5] As Levine reports, case definition requiring evidence of infection or exposure is problematic given the high rates of asymptomatic infection and the availability and uncertainties surrounding current testing.[19] The recent systematic review from Radia et al reports 42% (257/619) of cases as lacking PCR or serological evidence.[2] One of 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, were far more likely to lack PCR or serological evidence.[18] Data from UK intensive care PIMS-TS admissions reports 45 of 78 patients (58%) with evidence of current or prior SARS-CoV-2 infection. Importantly, data from this UK group and from Dufort's case series from the USA show no difference in clinical or biochemical parameters between those with and without PCR or serological evidence of SARS-CoV-2. [20,21]

Despite evidence for faecal shedding of SARS-CoV in the stool for up to 30 days PCR testing was negative in our patient.[22] 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.[2,23,24] Calprotectin has been shown to be a biomarker of gastrointestinal inflammation in COVID-19 without directly correlating with faecal ribonucleic acid (RNA) levels.[25] Multiple infection screens were negative and the clinical picture was not in keeping with an ulcerative colitis flare.

Overall, two thirds of reported cases required intensive care admission or ionotropic support.[2] However this likely represents the more severe end of the PIMS-TS spectrum. Belhadjen described 35 cases who required intensive support, including a third with extracorporeal membrane oxygenation (ECMO) requirements.[7] Most children have responded well to the different treatment regimens. At least ten fatalities in PIMS-TS have been reported to date.[2,16]

While our patient clearly met the UK case definition for PIMS-TS (recurrent fever, hyperinflammatory biomarkers, mucocutaneous, gastrointestinal, renal and haematologic involvement) the lack of PCR or serological evidence of SARS-CoV-2 infection does introduce a degree of uncertainty, as is present in up to 50% of cases, around the diagnosis. Epidemiologically, the timing of disease in this case does follow from the onset of the outbreak in the patients' locale and with potential exposure from an affected sibling. Antigen

and antibody testing was not available for the household contacts and T-cell specific testing, which may have benefits over antibody testing, was not available for the patient.[26] The timing of onset, the distinct constellation of clinical and biochemical features, the response to therapy and the lack of any other viable diagnosis despite an exhaustive inpatient search lasting several weeks does we feel support PIMS-TS as the most likely diagnosis.

The clinical phenotype in this case was less severe than the majority of cases reported to date. While it is certainly possible that this simply represents the milder end of the PIMS-TS spectrum, we speculate that maintenance anti-TNF-α therapy may also have contributed to the less severe disease course. Infliximab has a terminal half-life approximating ten days (on 5mg/kg dose) with prolonged bioavailability and accumulation on repeated dosing so would still have been present at time of presentation.[27,28]Infliximab also potentially interferes with serological testing for the condition. A caveat from manufacturers of serology testing at our institution is to interpret with caution in patients receiving treatment with preparations involving mouse monoclonal antibodies.[13] 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.[29] 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.[30] HAMA's may be distinct from anti-drug antibodies (ADA) which had not been detected previously in our patient.[31] It is important to be aware of this caveat and it may in part explain the negative serology in this case.

There is no established consensus on management of PIMS-TS. IVIG, corticosteroids and less frequently biologicals have been used in a variety of combinations with varying success.[2,6,16,20,21] Of note, infliximab is used successfully to treat the related condition of Kawasaki's disease.[32] Aspirin and heparin-based products have been administered for anti-inflammatory purposes and in view of concerns around increased thromboembolic risk.[1,33]

Evidence supporting the role of TNF-α in this disease comes from a case report from Dolinger who showed rapid clinical improvement with infliximab in a patient with PIMS-TS, in the context of co-presentation with newly diagnosed Crohn's disease.[34] Concerns around adverse outcomes associated with anti-TNF-α treatment and COVID-19 are not supported by current evidence.[35,36] Evidence implicating a key role of TNF-α in the immune mediated sequalae of COVID-19 are accumulating.[33,37,38] There is growing evidence around the role for corticosteroids in managing the immunological complications of SARS-CoV-2 infection, although it is not clear in PIMS-TS. [2,20,39,40] Our patient showed a prompt response to high

dose intravenous corticosteroids, and we hypothesise that anti-TNF-α before and after steroid therapy may have potentially reduced the severity of the disease in this case and contributed to the sustained clinical resolution.

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 has a wide, evolving spectrum and so requires a high index of suspicion. It must be added to the list of differentials for paediatric patients, with and without IBD, who present with recurrent fever along with inflammation on a multisystemic level. Gastrointestinal symptoms may be prominent along with elevated faecal calprotectin levels. Serologic testing may be negative in up to half of PIMS-TS cases, especially 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 as well as steroids 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.(Includes relevant negative investigation study summary)

		Result	Reference	On day*
Hb	(min)	**65**	115-155 g/L	37
Platelet	(min)	**323**	150-400 $x10^9$/L	33
White cell	(max)	**23.7**	4.5-14.5 $x10^9$/L	42
Neutrophil	(max)	**18**	1.5-8 $x10^9$/L	18
Lymphocyte	(min)	**0.5**	1.5-7 $x10^9$/L	30
CRP	(max)	**206**	0-5 mg/L	19
ESR	(max)	**>130**	mm/hr	29-36
Ferritin	(max)	**691**	15-80 µg/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

		Result	Reference	On day
Sodium	(min)	**136**	132-144 mmol/L	21
Creatinine	(max)	**86**	26-57 µm/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 µg/mL	6wks prior
Anti-drug antibodies		**nil**		6wks prior
Faecal calprotectin		**1020**	<200 µg/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**		

**Day of fever*

{Addendum: other relevant negative investigations included but not limited to:
Multiple (>3) respiratory infective screens using antigen testing and multiplex PCR on nasal/throat swabs – includes mycoplasma. Multiple (>3) infective stool screens - including viral, bacterial and parasitic screening with antigen, PCR and microbiological testing. Multiple (>3) each of blood and urine cultures.
Hepatotrophic viral screening – including for Hepatitis B, C, CMV, EBV, HSV, VZV, adenovirus on multiple test modalities.
Crytococcal and mycology screening with antigen and culture based testing.
Quantiferon gold, Mantoux testing and multiple chest X-rays.
Anti-streptolysin O titre – equivocal at 400IU/mL (<200IU/mL) but without change in serial measures.
Normal lymphocyte subsets and IgG subclasses, normal lymphoid population analysis by flow cytometry on bone marrow.
Urinary beta-2 microglobulins normal.
Normal Immunoglobulin A, D, M, E levels, normal neutrophil function testing, normal autoinflammatory and monogenic IBD genetic panels.

Autoimmune/vasculitides/rheumatology screening panels negative, including but not limited to ENA, ANA, ANCA, rheumatoid factor, anti-double stranded DNA antibodies, serum Angiotensin Converting Enzyme. HLA and clinical screening for Bechet's disease negative.}