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Multi-Systemic Inflammatory Syndrome in Children

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Abstract

The objective of our work is to study the multi-systemic inflammatory syndrome (PIMS) in children, to determine its frequency, by analyzing the epidemiological, clinical, paraclinical, therapeutic, and evolutionary profile of these patients. A retrospective study spanning a period of 2 years from April 2020 to March 2022. It concerns all children under the age of 16 admitted and cared for in the pediatric emergency department of the university hospital Hassan II of Fez for multi-system inflammatory syndrome (PIMS). Twenty cases of PIMS were collected over this period. Multi-system inflammatory syndrome in children has been described in temporal association with COVID-19, usually within 2 to 6 weeks of illness or exposure. The age of the patients varies between 8 months and 15 years. All patients presented with fever and cutaneous signs, followed by digestive signs and neurological signs. The inflammatory syndrome is frankly positive in all patients who had a COVID-19 PCR and/or positive serology. The treatment is based on the administration of immunoglobulins in association with corticosteroid therapy and non-specific antibiotic therapy in the majority of cases (80%). The evolution was favorable. PIMS should be considered in all children presenting with a clinical and/or biological inflammatory syndrome associated with COVID-19.

Keywords

Multisystemic Inflammatory Syndrome, Child, COVID-19, PIMS

1. Introduction

After the first wave of the 2019 coronavirus (COVID-19) pandemic, clusters of children with unusual multi-system inflammatory conditions emerged. PIMS childhood multi-system inflammatory syndrome is a recently identified condition that follows exposure to SARS-CoV-2. Although it has some similarities

with Kawasaki disease, it has its own epidemiological, clinical, biological, radiological, therapeutic, and evolutionary characteristics that make it a distinct entity. The definition of a case of PIMS proposed by the World Health Organization (WHO) is based on well-codified criteria [1].

Our work of analyzing the files of patients with multi-systemic inflammatory syndrome in children, over a period of two years from April 2020 to March 2022, was cared for in the pediatric emergency department of the university hospital HASSAN II in Fez. The objectives of the study were to study the epidemiological, clinical, biological, and radiological aspects, the evolutionary profile of our patients, and the development of the literature review for this PIMS syndrome.

2. Materials and Methods

Our work consists of a retrospective, descriptive study of the files of children admitted and cared for PIMS, in the pediatric emergency department of the university hospital Hassan II Fez, over a period of 2 years, from April 2020 to March 2022. We included in our study all patients followed in the department, admitted and treated for PIMS whose diagnosis was confirmed according to WHO recommendations, and who were under 16 years of age. The patient inclusion criteria were selected following WHO recommendations are children and adolescents aged 0 to 19 years with fever > 3 days, and two of the following signs: Rash, bilateral non-purulent conjunctivitis, signs of mucocutaneous inflammation, hypotension, shock, signs of myocardial dysfunction, pericarditis, valvulitis, coronary abnormalities, signs of coagulopathy or acute gastrointestinal disturbances. Its clinical signs are associated with elevated inflammatory markers with no other obvious microbial cause of inflammation and evidence of COVID-19 infection or likely contact with COVID-19 patients. Patients excluded from our work are those whose records are incomplete and who do not meet WHO recommendations. The collection of data was established retrospectively from patient files in paper form and in computerized form and from patient follow-up registers. The various parameters studied are anamnestic, age at diagnosis, sex, origin, and history. As well as clinical characteristics such as fever, rash, inflammatory syndrome, cardiac involvement, clinical neurological signs, paraclinical elements, complete blood count, inflammatory assessment, serological and/or COVID-19 antigen test, cardiac assessment, therapeutic elements, and evolution.

3. Results

During the period of our study, we collected 20 cases of multi-systemic inflammatory syndrome in children, who met the inclusion criteria, and who were treated in the pediatric emergency department of the CHU Hassan II Fez. The recruitment of patients remains very variable from one month to another with a maximum of cases found in August 2021 (n = 4). The first case admitted to the emergency room was in October 2020. The recrutment prevalence pattern fol-

lows a curve with an aspect of two waves following the waves of the pandemic. The age of the patients in our series at the time of diagnosis varies between 1 and 15 years, with an average of 6 years and a Sex-ratio M/F of 1.8. Contact with a person with COVID-19 was sought in all our patients and was only reported in nine cases, two of them with parental contact. None of the cases presented with comorbidities, such as heart disease, thromboembolic diseases, diabetes, and obesity (Table 1). The consultation time varied from two days to two weeks with an average consultation time of five days. The time between contact with a COVID-19 case and the appearance of clinical signs was eight weeks on average, with extremes ranging from three to ten weeks. The symptoms motivating the consultation in our series are dominated by prolonged fever and digestive signs. It should be noted that some of our patients had an association of several signs (Table 1). The mean duration of the fever was six days, varying between five and seven days, with a mean temperature on admission of 38.95˚C. Digestive signs are present in 70% of patients (n = 14). These signs are represented by abdominal pain in (50%) of ten children, vomiting in six (33%) cases, and diarrhea in (55%) 11 children. Cutaneous signs (Figures 1-4) are represented by a rash in 20 patients (100%), Morbilliform type in 12 cases (60%), or Scarlatiniform in eight children (44%). Bilateral non-purulent conjunctivitis was present in eight patients (44%). Pharyngitis was found in seven patients (35%). Involvement of the oral mucosa was observed in10 patients (50%). Neurological impairment in three cases (one case had headaches and two cases of convulsive crisis with impaired consciousness). The other symptoms are represented by generalized fatigue or myalgia with the notion of arthralgia in seven cases. Respiratory involvement is represented by polypnea in three children. Examination of the lymph nodes revealed centimetric later cervical adenopathies in eight cases. Table 1 presents the epidemiological profile and clinical presentation of children treated for PIMS.

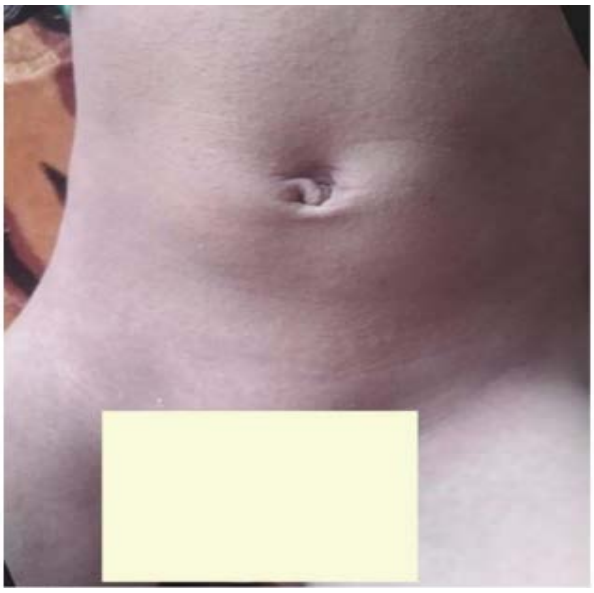


Figure 1. Scarlet-like eruptions on the trunk, feet and back with fine scaling on the seat.

Table 1. Epidemiological profile and clinical presentation of children treated for PIMS.

	Number of cases	Percentage
Epidemiological characteristics		
Sex:		
- Girls	7	35%
- Boys	13	65%
Age range		
- 1 - 2 years old	3	15%
- 2 - 5 years old	6	30%
- 5 - 10 years old	6	30%
- 10 - 15 years old	5	25%
Case history:		
- Contact with a positive case	9	45%
Clinical signs:		
Fever:	20	100%
Digestive disorders:		
- Vomiting and nausea	10	50%
- Abdominal pain	14	70%
- Diarrhea	11	55%
Respiratory disorders:		
- Polypnea	3	15%
Cardiovascular disorders:		
- Tachycardia	2	10%
Neurological disorders:		
- Headache	1	05%
- Signs of encephalitis	2	10%
Mucocutaneous signs:		
- Bilateral dry conjunctivitis	8	40%
- Cutaneous rash	20	100%
- Pharyngitis	7	35%
- Involvement of the oral mucosa	10	50%
- Cheilitis	8	40%
- Edema of the extremities	2	10%
Other signs:		
- Fatigability and myalgia	7	35%
- Presence of cervical adenopathy	8	40%

Table 2. Results of laboratory tests, treatment and outcome in children treated for PIMS.

	Number of cases/disturbed or abnormal	Percentage
Biological check-up:		
BC:	20	100%
- Anemia	20/13	100%/65%
- Hyperleukocytosis	20/13	100%/65%
- Lymphopenia	20/13	100%/65%
- Thrombocytopenia	20/6	100%/30%
- Thrombocytosis	20/0	00%
Markers of inflammation:		
- CRP	20/20	100%/100%
- SV	20/20	100%/100%
- Ferritin	20	100%/100%
- Fibrinogen	6/4	30%/20%
Liver function tests:		
- Transaminases	20/12	100%/60%
- TP/TCA	20/1	100%/5%
- Hypo albuminemia	20/6	100%/30%
Lipid profile:		
- Triglycerides	20/10	100%/50%
- HDL-C	20/1	100%/5%
Renal function:	20/0	100%/0
Cardiac work-up:		
- Toponin	3/0	15%
- D-dimer	9/8	45%/40%
- NT-ProBNP	0	0
COVID-19 work-up:		
- COVID-19 RT-PCR	20/4	100%/20%
- COVID-19 viral serology	16/16	80%/80%
Other tests:		
- Lumbar polction	3/0	15%
- ECBU	20/0	100%/0
- Blood culture	16/0	80%/0
- Tumor lysis syndrome	7/0	35%/0
- CMV and EPV viral serology	13/0	65%/0

Continued

- Typhoid fever serology	6/0	30%/0
- Blast count	5/0	25%/0
- Lipasemia	8/1	40%/5%
Radiological work-up:		
- Radiography	20/0	100%/0
- ETT	7/0	35%/0
- Abdominal ultrasound	5/2	25%/10%
- Abdominal CT scan	2/2	10%/10%
- Cerebral CT/MRI	2/0	10%/0
Management:		
- IV Ig	20	100%
- IV or oral corticosteroids	9	45%
- Antibiotics	20	100%
- Salicylic acid	4	20%
- Antipyretics and analgesics	18	90%
- Vitamin complex	7	5%
- Anticoagulant	1	

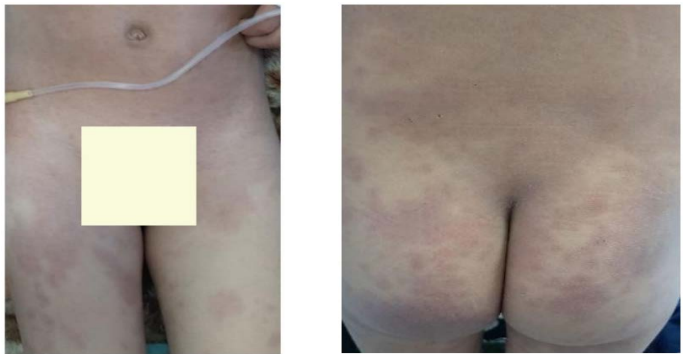


Figure 2. Morbiliform rash on the trunk, back, lower limbs and seat.

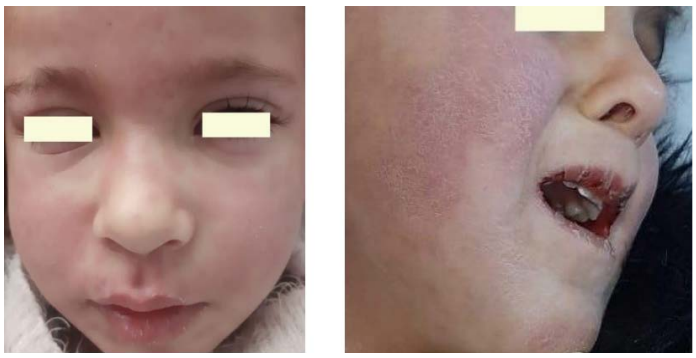
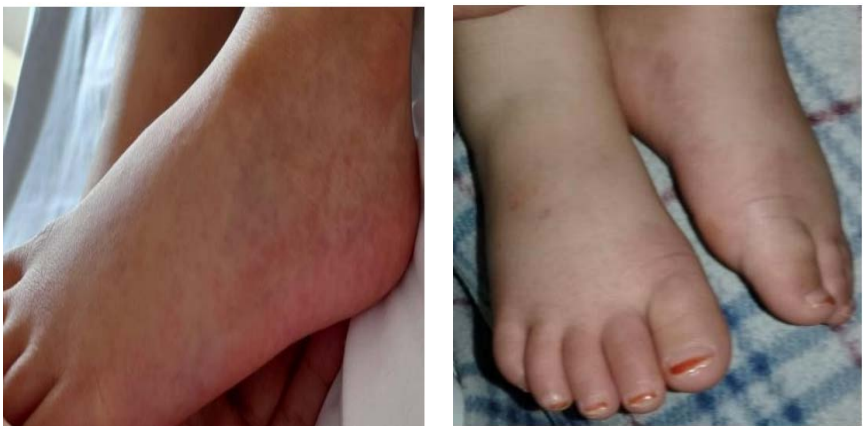


Figure 3. Facial rash with cheilitis in two of our patients.



(a) (b)

Figure 4. (a): Plantar and foot rash in one of our patients. (b): Edema of the extremities in one of the patients in our study.

In our study, the biological assessment was done at the time of admission to the emergency room in all patients (**Table 2**). The assessment carried out was an Blood count (BC), an inflammatory syndrome, and a cardiac assessment. The other assessments were carried out in front of the prolonged fever, to eliminate the differential diagnoses (urinary tract infection, macrophage activation syndrome, malignant hemopathy, typhoid fever, etc).

BC was performed as the first intention in all patients, objectifying anemia in 13 children as well as hyperleukocytosis predominantly of neutrophils, Lymphopenia in 13 children and thrombocytopenia in six patients or 25%. CRP was elevated in 100% of cases, with a median value of 214 (99.1 - 285.5) mg/L. The sedimentation velocity was accelerated in all children, with a median value of 62.5 (40 - 70) mm/h. Blood ferritin assay showed hyperferritinemia in 100% of cases with a median value of 495.5 (300.5 - 1080) µg/L. Fibrinogenemia was performed in six children and it objectified hyperfibrinogenemia in four which varies between 4.69 and 4.86 g/L. Transaminases were performed in 20 children, they were disturbed in 12 cases. PT was decreased in one case and TCA was normal in all patients. The albumin assay showed hypoalbuminemia below 30 g/L in six patients. Hypertriglyceridaemia was noted in 10 patients with a median of 4.15 (2.68 - 4.83) g/L. Renal function and an ionogram were performed as part of the assessment of the impact and they did not show any abnormality. Troponin was negative in the three patients for whom results are available. Increased D-dimers were noted in eight out of nine patients, with a median value of 2060 (574.5 - 4475) ng/mL. The PCR test was performed for all patients and was positive in four patients. COVID-19 IgG/IgM serology was performed in all children and IgG was positive in all patients. The other assessments carried out in the patients of our study are the ECBU in all the children returned sterile. Blood cultures are performed in 16 children returning sterile after 72 hours. The lumbar puncture was performed in three children and came back negative. The search for a plastid and a smear was made in five children. The tumor lysis syndrome

assessment was carried out in seven children and returned to normal. CMV and EBV serologies were performed in 13 children returning negative. Serology of typhoid fever in six children. A lipasemia was done in eight children with intense abdominal pain that was greater than 3 times normal in one child.

Chest radiography was normal in all patients. Abdominal ultrasound was performed in five children and abdominal CT was performed in two patients. Ultrasound findings were low abundance peritoneal effusion in one case and mesenteric lymphadenopathy in one case and normal return in three children. CT was in favor of pancolitis with lymphadenopathy in one case and Balthazar's stage C pancreatitis in one case. The cerebral MRI was requested in the two patients having presented disorders of consciousness, it came back normal. Trans-thoracic echocardiography (ETT) is not common practice, given the period of the pandemic, its realization was not always possible, three children benefited from ETT during the hospitalization and who came back normal. It was made in four children after a period of two weeks.

The diagnosis of PIMS was retained in our patients based on the initial somatic examination, a biological assessment, and a serological assessment.

Hospitalization is the rule in case of prolonged fever in all our patients. The action to be taken in an emergency initially consisted of conditioning the patients under monitoring and monitoring of saturation and temperature in rooms dedicated to patients with COVID-19. Treatment can combine corticosteroid therapy, immunoglobulin, antisludge, anticoagulants, and antibiotics (ATB) depending on the clinical severity of the syndrome. In our series, administration of a high dose of polyvalent immunoglobulin intravenously was the rule in all patients, at a dose of 2 g/kg. For injectable corticosteroid therapy, nine patients received boluses of corticosteroids Methyl-prednisolone (Solumedrol*) at a dose of 1 mg/kg/12h for three to five days then relayed orally for a total duration of one week. The oral route was recommended from the outset in three children. Acetylsalicylic acid was used in four children. Corticosteroid therapy is administered to eight children. All patients in our study were put on empirical antibiotic therapy based on Azithromycin and/or 3rd generation cephalosporin. Injectable ATB was put in 16 children, this ATB stopped within 48 hours in four patients and 10 days were totaled in 12 children. Azithromycin was administered from the outset in the four children with positive PCR. Oxygen was not required in any of our patients. A patient presented a picture of encephalitis, he was administered acyclovir. Seven patients were put under a combination of Vitamin C, Vitamin D, and Zinc, those with fatigability and myalgea (Table 2).

The average hospital stay was nine days ranging from five days to 12 days. The short-term evolution was favorable in all cases. There was an improvement in clinical systemic damage and markers of inflammation. Apyrexia was obtained between two and six days after the start of treatment, with an average of six days. In our study, the digestive signs were completely resolved during hospitalization, after four days on average with cases up to 10 days. The regression of the mucocutaneous signs was obtained from the second day and a total resolution after

seven days in all the children. The evolution of neuromuscular signs was favorable in all patients. The patient, who had presented a picture of encephalitis, returns to a normal state of consciousness in five days with a good improvement after 10 days.

Biological evolution was marked by a gradual decrease in the inflammatory syndrome with normalization of CRP, fibrinogen, and SV over a period ranging from the end of the first week to six weeks. Normalization of the blood counts after two weeks on average. The medium-term evolution was favorable in all patients with follow-up in consultation. Furthermore, no patient was readmitted to the service during the follow-up, nor any infectious or other complication was observed and no death was declared among our patients.

4. Discussion

The PIMS or MIS-C or Kawasaki-like disease is a new severe pediatric systemic inflammatory syndrome, which appeared in the epidemic context of COVID-19 infection. Three definitions exist: PIMS (Royal College of the United Kingdom) [2], MIS-C (CDC in the United States) [3], and Multisystem inflammatory syndrome in Children and Adolescents (WHO) [1]. In practice, we use the three definitions mixed. The case definition of PIMS proposed by the WHO is based on having a fever for three days or more and having at least one of the following two signs [1]: Skin rash or Bilateral nonpurulent conjunctivitis or signs of mucocutaneous inflammation, Hypotension or shock, Signs of myocardial dysfunction, pericarditis, valve disease or coronary abnormalities, Signs of coagulopathy, Acute gastrointestinal disturbances. Its signs are associated with elevated inflammatory markers with no other obvious microbial cause of inflammation and evidence of COVID-19 infection or likely contact with patients with COVID-19. According to various studies, PIMS occurs four to six weeks after an acute COVID-19 infection [4].

This condition is uncommon. In New York, the prevalence of PIMS has been estimated at two cases per 100,000 people under the age of 21, while over the same period, the prevalence of infection with SARS-CoV-2, in the same age group, was 322 per 100,000 [5].

In France, 254 potential cases of PIMS were identified by "Santé Publique France" between March 16, 2020, and November 17, 2020, out of a population of 16.4 million people under the age of 20 [6].

Using the available literature and the guidelines of international institutions, the recommendations for the management of PIMS-TS represent the best results based on the knowledge currently available to facilitate and standardize the treatment of children suspected of PIMS-TS. The available literature is limited to retrospective and prospective studies from different regions of the world. No trials are comparing the different treatment modalities. Recommendations on the use of various immunomodulatory agents, therefore, are limited to data from these observational cohort studies and indirect evidence from other hyperinflammatory conditions in children and adults.

In our study, the median age was 6 years with a sex ratio of 1.8. Our results concerning age and sex in children with PIMS were close to those found in the various international studies [7] [8] [9] [10].

The various studies published in the literature incriminate the interaction of several comorbidities associated with PIMS, among these comorbidities reported in the majority of cases were obesity and asthma. In Feldstein's series, 27% of cases had comorbidities, of which 29% of cases are obese, 18% of cases are followed for respiratory pathology, and 3% are followed for cardiac pathology [8]. According to Whittaker *et al.*, 25% of cases were obese and 12.5% of cases are asthmatic [7]. In our study, none of the children had a particular risk factor.

Most children with COVID-19 have a range of signs and symptoms that are not severe or specific enough to warrant testing or treatment. Some children and adolescents have no symptoms. The problem with cases of asymptomatic children with undetected COVID-19 is that they could become silent carriers in the community or be at risk of developing post-COVID-19 complications. Although early data suggests that COVID-19 causes mild illness in children, several centers in Europe and the United States have identified a new hyper-inflammatory syndrome associated with this infection, known as multisystem inflammatory syndrome, known as pediatric multisystemic inflammatory syndrome, also known as pediatric multisystemic inflammatory syndrome with a temporal link to SARS-CoV-2 or PIMS-TS. Multisystemic inflammatory syndrome in children is a febrile syndrome characterized by multisystemic hyperinflammation, persistent fever, and dysfunction of multiple organs [8] [11]. The similarities in clinical-biological presentation, the lack of knowledge of the disease at the start of the epidemic and the fact that the "PIMS" code is not referenced in the ICD 10 (International Classification of Diseases) explain the over-representation of this coding in the first term. In the American study, out of 186 cases, 40% had a picture compatible with MK according to the criteria of the American Heart Association, half of whom had diagnostic criteria for complete MK and the other half for incomplete MK [8].

The series of Pouletty *et al.*, Dufort *et al.*, and Feldstein *et al.* report an exposure interval, respectively: 21 days, 25 days, and 21 days [4] [5] [12]. In our series, the interval between contact with patients with COVID-19 and the onset of PIMS in our patients varies between one and four weeks with an average of 21.4 days.

In our study, the clinical picture was fever and skin involvement in all children and digestive signs in 70% of cases. In the series of Pouletty *et al.*, 94% of patients developed mucocutaneous signs and digestive manifestations in 81% [4]. For Verdoni *et al.* 70% of patients present at least one mucocutaneous sign [13]. In the series Dufort *et al.*, the clinical signs are represented by digestive manifestations in 80% of cases, including 75% by abdominal pain, 72% by nausea and/or vomiting, and 62% by diarrhea [5]. The Hajiani and Encinosa series respectively report digestive manifestations in 26% of cases and 44.2% of patients [9] [10]. Cardiac involvement has only been reported in certain series in the li-

terature [4] [5] with percentages varying from 69% to 36%. Neurological signs resulting from PIMS appear to be quite common in many studies [4] [5] [14] [15]. In our patients, neurological signs are present in three children (25%). The respiratory manifestations seem to be absent and are only presented by a slight polypnea in three children (25%), however many studies differ on this parameter [4] [5] [8] [15] and this seems to be due to the inclusion criteria which differ from one study to another.

The abnormalities of the blood count reported in the various studies carried out within the framework of the PIMS are, a high neutrophil count, lymphopenia, deep anemia, and a low platelet count, [5] [7] [8] [10] [16] which agrees with the results of our work. The hyper-inflammatory character of PIMS is easily appreciable with a high CRP and an accelerated ESR [4] [5] [10] [16] [17].

The thromboembolic risk of PIMS is biologically objectified in our series. The assessment showed an increase in D-dimers in 87.5% of cases and hyperfibrinogenemia in four children. These results are consistent with those of the literature [5] [8] [16] [17]. In our study, all patients had positive COVID-19 serology, at admission, to IgG (100%) and four patients had simultaneous PCR and positive serology. There were no significant differences in other laboratory characteristics between the patients in our study and what is reported by the other studies [7] [14] [18] [19] [20] [21].

Cardiac markers and transthoracic echocardiography (ETT) are not common practice, At least one ETT was requested, given the period of the pandemic, its realization was not always possible, three children benefited from ETT during the hospitalization and which came back normal, and it was made in four children after a period of 2 weeks. For the results of the literature, cardiac involvement has been reported in several series [8] [17] [22].

Treatment algorithms have been developed by learned societies (the French Pediatric Society and the steering committee of the COPIL Covid inflammation group and the American College of Rheumatology) [11] [23]. Comparing our results with the results of other studies, the results are generally consistent. In our study, the administration of immunoglobulins was all children. THE Immunoglobulins are associated with corticosteroid therapy in nine cases or with NSAIDs in four cases. ATB was administered to all patients for two reasons our country has adopted a protocol against COVID, the treatment of which combines an ATB based on Azithromycin in addition to a vitamin complex. Injectable C3G cephalosporins were started in 16 children, stopped within 48 hours in four patients, and 10 days totaled in 12 children. The second difference was the use of acetylsalicylic acid which was only administered to four children because in our management we relied on algorithms and the children in our series did not have thromboembolic risk factors (obesity or heart disease, etc.)

Most children with PIMS in published studies were seriously ill and required intensive care. Although most patients with PIMS required intensive care and immunomodulatory therapies, favorable outcomes were observed with low mortality (<2%) [24]. The need for care in an intensive care unit was similar

even in our study because the action to be taken in an emergency initially consisted of conditioning the patients. Sub-monitoring and saturation monitoring and temperature in the presence of a respirator and medical emergency equipment, in rooms dedicated to patients with COVID-19. The evolution was favorable in all the patients of our short-term and medium-term study.

5. Conclusion

Childhood multisystem inflammatory syndrome PIMS is a recently identified condition that follows exposure to SARS-CoV-2. Although it has some similarities with Kawasaki disease, it has its own epidemiological, clinical, biological, radiological, therapeutic, and evolutionary characteristics which make it a distinct entity. This syndrome should be suspected in any young child with persistent fever for more than 3 days, gastrointestinal symptoms, skin and mucous membrane involvement, and/or signs of shock. Intravenous immunoglobulin and systemic corticosteroid therapy are the mainstay of treatment. Long-term patient outcomes are limited in the literature; however, early reports are encouraging.

Conflicts of Interest

The authors declare no conflict of interest.

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