Pfeifer-Weber-Christian Disease: A Case Report and Review of Literature on Visceral Involvements and Treatment Choices

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ABSTRACT: Pfeifer-Weber-Christian disease (PWCD) is a rare idiopathic disease characterized by lobular panniculitis of adipose tissue with systemic symptoms and multiple organ involvement. Even though the systemic involvement is rare, it is life-threatening and represent a treatment challenge for the clinicians. We report a case of PWCD characterized by hepatic, hematologic, and renal involvement, with good response to mofetil mycophenolate and prednisone treatment. A 47-year-old female presented several months' history of painful subcutaneous nodules, fever and lymphadenopathy with recent appearing of microcytic hypochromic anemia, leucopenia with neutropenia, and increase in transaminase. Skin biopsy showed lobular panniculitis with lymph-histiocytic and neutrophilic infiltrates with necrosis of adipocytes. A combination therapy of corticosteroid with mofetil mycophenolate was effective. Moreover, we discuss the clinical manifestation and the therapeutic choices in PWCD, from classical immunosuppressive drugs to new biotechnological agents, and we provide a comprehensive review of the available literature.

KEYWORDS: Pfeifer-Weber-Christian disease, hematologic dyscrasia, nonalcoholic fatty liver disease, pleural effusion, liver biopsy, mycophenolate mofetil

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Introduction

Pfeifer-Weber-Christian disease (PWCD) is a rare illness of unknown etiology, with a higher prevalence in female. It is characterized by recurrent fever associated with the appearance of single or multiple nonsuppurative nodules, sometimes tender, due to an inflammatory process associated with subcutaneous tissue necrosis.[1] In many cases, further lesions subsequently appear elsewhere in the panniculus adiposus.[2] Several cases with hepatomegaly or splenomegaly and changes in liver function have been published.[3-7] Systemic symptoms and signs such as relapsing fever episodes, fatigue, and polyarthralgia are also frequent. On the contrary, hematological abnormalities and visceral involvement of organs including lungs, heart, intestines, spleen, kidneys, and adrenal gland are rarely described.[2,5,8-11] We report herein a case of a patient with PWCD showing hepatic (nonalcoholic fatty liver disease [NAFLD]), hematological, renal, and serosal involvement, which were resolved by the administration of prednisone and mycophenolate mofetil. This case report is presented after informed and signed consensus of the patient in study.

Case report

A 47-year-old Caucasian woman was admitted to our Rheumatology Unit, complaining a 6-month history of progressive appearance of tender ill-defined hard swellings on the right leg and the abdominal wall with severe erythema in overlying skin, associated with intermittent fever up to 39°C, not relieved by antipyretics and antibiotics.

The patient had fever up to 39°C, multiple tender erythematous swellings on abdomen wall and right leg, and several palpable lymphadenopathies on abdomen, neck, and right groin during admission to our Unit. She denied drug abuse, recent travel, or use of nonsteroidal anti-inflammatory drugs. Complete blood count revealed microcytic hypochromic anemia with hemoglobin 9.8 gm/dL, mean corpuscular volume 69 fl, and leucopenia with neutropenia (WBCs 1.3×10^3/L; N 48.3%, L 43.8%, M 3.8%, E 0.4%, B 2.2%).

Thrombocytopenia (up to 67000/μL) had been briefly observed during the recovery period. There was an increase in alanine transaminase (ALT) 104 IU/L (normal range, 2-40) and aspartate aminotransferase (AST) 91 IU/L (normal range, 2-40), with an AST/ALT ratio < 1 and an increase of gamma GT 67 IU/L (normal range, 7-38). A slightly high serum lipid profile (triglycerides, total cholesterol, and low-density lipoprotein) was observed. Erythrocyte sedimentation rate (ESR) was 17 mm/h, C reactive protein (CPR) was 0.05 mg/dL. Normal immunoglobulin assay except high levels of IgM 443 mg/dL (n. 40-230) and of IgE 857 mg/dL (n. 2-200) was noticed. Complement 3, complement 4, cryoglobulin levels, serum lipase, serum amylase, α-1 antitrypsin, procalcitonin, haptoglobin, creatine phosphokinase, creatinine, azotemia, serum glucose concentration, bilirubin and bilirubin fraction, serum

corrected calcium, and alkaline phosphatase were within normal range. Antithrombin was mildly elevated, 165% (normal range, 70-130). Severe hypofibrinogenemia 40 mg/dL (normal range, 200-450) with high levels of D-dimer 23 701 µg/mL (normal range, 0-500) were detected. The 24-hour urinary sample showed moderate proteinuria (1.6 gm/24 h). An increase of lactate dehydrogenase (LDH) 500 IU/L (n. 40-250) and beta-2 microglobulin 7.34 µg/mL (normal range, 0.8-2.7) was revealed. Partial thromboplastin time (PTT) was shorter. Prothrombin time and iron profile were normal. Albumin level was 3.2 gm/dL. A hypergammaglobulinemia (23.78%) was noted by protein electrophoresis. Serum and urine immunofixation were negative for free light chains. TORCH screening, tuberculosis screening, Coxsackie IgM, Brucella IgG and IgM, Borrelia IgG and IgM, and Parvovirus B19 were negative. The antinuclear antibodies, lupus anticoagulant screening, antineutrophil cytoplasmic antibodies, cryoglobulin, and antiphospholipid antibodies were negative. Viral hepatitis, autoimmune hepatitis, metabolic factors and in-born or hereditary disorders (Wilson disease, lypodystrophy), drug and toxins associated to high liver enzymes and excessive alcohol consumption, obesity, and diabetes mellitus were excluded.

A mild hepatosplenomegaly with widespread lymphadenopathy and left pleural effusion were detected using sonography and confirmed by neck, chest, and abdomen computed tomographic scan. The echocardiography detected a small pericardial effusion, with normal eject fraction and preserved systolic function. The endocrine and genital organs and the breast showed no clinical abnormalities.

Surgical skin sample showed lobular panniculitis with a lymph-histiocytic and neutrophilic infiltrates with necrosis of adipocytes, as seen in PWCD.

Bone marrow biopsy displayed a discrete hypercellular bone marrow with an increase of megakaryocytic proliferation and low grade of dysmorphia of myeloid cells. A widespread boost of stromal fibers was noticed at silver impregnation. The marrow changes were reactive and did not reflect a myelodysplastic syndrome.

Axillary lymph-node biopsy confirmed a reactive lymphadenopathy. The hematological specialist excluded hematological malignancies.

The liver biopsy evidenced a macro-vesicular steatosis with hepatocytes ballooning, as in NAFLD. Spotty necrosis, scattered mixed neutrophilic-lymphocytic inflammation, Mallory hyaline, and perisinusoidal fibrosis were absent.

On admission, levofloxacin (750 mg daily) and minocycline (200 mg daily) were empirically started and discontinued after 8 days for negative blood cultures. Mycophenolate mofetil (MMF) (2 gm daily) and prednisone (1 mg/kg daily, tapered to 5 mg daily in 3 months) were started. At 1-month follow-up, the improvement of skin lesion, the remission of fever, and complete normalization of blood count, proteinuria, and liver enzymes were recorded. A complete remission state, with just slightly hyper-pigmentated skin scares, was recorded at sixth month follow-up.

Of note, considering the prompt remission of proteinuria after prednisone and mycophenolate mofetil treatment, the kidney biopsy was not more performed.

Discussion

PWCD is an inflammatory disease characterized by a wide spectrum of clinical manifestations, ranging from skin lesions and adipose tissue abnormalities, to systemic involvement.

The skin-limited form of the PWCD, also known as "relapsing febrile non-suppurative nodular panniculitis", well describes the principal clinical triad of pyrexia which varies widely in degree, panniculitis, and the tendency to relapsing course.[12] It is rarely lethal and in most of the cases, it is described as a spontaneous remission.[13]

Systemic PWCD frequently affects the liver, the bone marrow, and the kidneys, sporadically the serosa, spleen, lungs, heart, and intestines.[9] It could be life-threatening, representing a treatment challenges for clinicians.

Systemic symptoms and signs such as relapsing fever episodes, fatigue, and polyarthralgia are also commonly encountered in both skin-limited and systemic PWCD form.[11,14,15]

An electronic literature search on PWCD visceral involvements and treatment choices was conducted using Google Scholar, Scopus, and PubMed. Case reports published up until 2019 were evaluated (Table 1).

Liver Manifestation

The liver is one of the most frequent organs involved in systemic PWCD. The liver manifestation consists principally in liver enlargement, moderate to severe increase of aminotransferase and LDH levels, and rarely in jaundice. Some cases of variceal bleeding due to extrahepatic portal hypertension from mass effect of fat necrosis and liver fibrosis have also been described.[25,26] The most common histopathologic finding reported is the different degree of macro-vesicular steatosis (sometimes contained foam cells),[19] with[1,3,4,6] or without[5] hepatocyte necrosis and mononuclear cells infiltration.[6] In some cases, the presence of Mallory bodies has been evidenced.[18] Oram and Cochrane first hypothesized that occasionally gross fatty metamorphosis can take place in the liver as well as in other organs and give rise to considerable enlargement, reporting a case of 63-year-old woman with hepatomegaly, steatosis (revealed by means of biopsy), and fever.[12] Now, PWCD is recognized among the metabolic abnormalities associated with NAFLD[27-30] and nonalcoholic steatohepatitis (NASH).[3,6,18,31] Wasserman et al[6] evidenced the difference between the NASH due to PWCD, characterized by an active inflammatory state and the elevation of the aminotransferase and especially the LDH levels and NASH due to obesity and diabetes mellitus. Enlargement of the portal area accompanied by inflammatory

Table 1. Overview of works derived from medical literature reporting treatment of systemic Weber Christian disease, with description of main clinical manifestation.

	NO. OF PATIENTS (AGE); DISEASE DURATION	SYSTEMIC SYMPTOM, VISCERAL INVOLVEMENT, COMORBIDITY	BLOOD COUNTS	BONE MARROW BIOPSY	LIVER BIOPSY	TRANSAMINASE	COAGULATION	KIDNEY DISFUNCTION	TREATMENT	OUT COME
Fukuoka et al.[1]	1 f (16 y); 5 months	Fever, Lymphadenopathy: paratracheal and mesenteric lymphadenopathies (dilated sinusoids filled with macrophages and giant cells); Hemorrhagic pleural and peritoneal effusion	Anemia	Macrophages infiltrate and presented a considerable retardation of the maturity of granulocytic series	Cells atrophy and marked fatty degeneration	—	Normal	Proteinuria	Steroids	Exitus for severe hemorrhage from the biopsied region
Milner et al.[5]	1 f (57 y); 13 months	Fever; left pleural and peritoneal effusion; pulmonary opacities	Anemia, thrombocytopenia	—	Periportal fatty change but no evidence of necrosis, inflammation or cirrhosis	—	—	—	Prednisone (80 mg/d with tapering)	Exitus
Henrikson et al.[16]	1 f (19 y); 24 months	Gastrointestinal and subcutaneous hemorrhages	Pancytopenia	—	—	↑ GOT and ↑ bilirubin (6-8 mg/100 mL)	↓ FBG, ↓factor XIII levels ↑ FDP, ↓ factor V, ↓plasminogen levels		Prednisolone at 90 mg/d with tapering, benzylpenicillin, tranexamic acid, aprotinin and heparin	Died from staphylococcal sepsis and intracranial hemorrhage
Mori et al.[17]	1 f (21 y); 33 months	Fever, tarry stools, epistaxis, vein thrombosis.	Pancytopenia	—	—	↑ GOT and ↑ GPT and ↑ bilirubin	↑ KPTT, ↓ PT, ↓ TT value, ↓ FBG	Proteinuria	Prednisolone (100 mg/d), blood transfusions and heparin iv	Well-controlled state
Allen-Mersh[3]	1 f (7 y); 11 y	Fever; splenomegaly; Comorbidity: herpes genitalis, diabetes mellitus and hepatic cirrhosis, amyloid deposit in pancreatic islets	Hypochromic anemia, leucopenia	—	Expanded portal tracts infiltrated with a mixture of inflammatory cells, including many plasma cells, combined with bile duct proliferation and disruption of the limiting plate. The parenchyma showed mild fatty change and nuclear vacuolation	—	—	—		Exitus for liver failure
Kimura et al.[18]	1 f (32 yrs); 51 months	Fever, hepatosplenomegaly.	Normal	—	Mallory bodies	↑ GOT and ↑ GPT	—	—	Prednisolone, 60 mg/d	Recurrent
Ciclitira et al.[19]	1 f (27 y)	Fever; Lymphadenopathy: reactive changes; rectal bleeding, jaundice	Slightly anemia and neutropenia	circumscribed foci of eosinophilic necrosis which were associated with many foam cells	Striking periportal fatty change with some very large fat vacuoles some of which contained foam cells	—	↑PT and ↑ TT	—	Prednisolone (30 mg/d)	Exitus for liver failure

(Continued)

Table 1. (Continued)

	NO. OF PATIENTS (AGE); DISEASE DURATION	SYSTEMIC SYMPTOM, VISCERAL INVOLVEMENT, COMORBIDITY	BLOOD COUNTS	BONE MARROW BIOPSY	LIVER BIOPSY	TRANSAMINASE	COAGULATION	KIDNEY DISFUNCTION	TREATMENT	OUT COME
Hotta et al.[20]	1 f (23 y); 3 y	Fever	Leucopenia	—	—	↑ GOT and ↑ GPT	Normal	Normal	AZA (150 mg/d)	Remission
Dupont et al.[13]	1 f (54 y);	Fever	Anemia	—	—	Normal	Normal	Proteinuria (membranous glomerulonephritis)	No treatment was instituted	Spontaneous remission
Kirch et al.[21]	1 m (31 y); 23 months	Arthralgia, fever, and fatigability.	Leukocytosis	—	—	Normal	Normal	Normal	Cyclophosphamide (200 mg daily)	Remission
Yoshimura et al.[11]	1 f (42 y); 8 y	Fever, muscular pain, multiple joint pain. Lymphadenopathy: swelling of cervical and inguinal lymph nodes, dermatopathic lymphadenitis. Comorbidity: Hashimoto thyroiditis.	Anemia and thrombocytopenia	—	Enlargement of the portal area accompanied by small round cell infiltration, piecemeal necrosis, bile duct proliferation and edema as well as fibrosis around the bile ducts were observed. Thickening and cell infiltration of branches of the hepatic artery suggestive of vasculitis were also found.	Normal	Normal	Proteinuria due to proliferative Glomerulo-nephritis	Prednisolone (20 mg/d), cyclophosphamide (50 mg/d)	Death due to gastro-intestinal bleeding
Enk et al.[22]	3 (55 y, 58 y, 49 y); 10 months	Fever, 2 pts also had inflammatory lesions in their retroperitoneal fat (assessed by magnetic resonance imaging)	Normal	—	—	Normal	Normal	Normal	MMF (2 g/d) in addition to prednisolone, Failure of AZA (1.5 mg/kg) and MTX (50 mg/wk).	Complete remission of skin and retroperitoneal lesions.
Wasserman et al.[6]	1 f (27 y); 5 y	Recurrent fevers	Leucopenia	—	Moderate centrilobular macro-vesicular steatosis with hepatocyte necrosis and mononuclear cell infiltration. Portal fibrosis and centrilobular pericellular fibrosis were observed	↑ GOT, ↑ GPT and ↑ γGT	Normal	Normal	AZA 125 mg daily and prednisone 20 mg/d	Good response with just 2 relapse episodes (AZA 50 mg/d)
Başkan et al.[14]	1 f (45 y); 10 months	Fever, malaise, and arthritis. Comorbidity: peptic ulcer and depressive syndrome.	Hypochromic and microcytic anemia	—	—	Normal	normal	normal	MMF (2 g/d). (Failure of prednisolone 1.5 mg/kg per d)	Complete remission

(Continued)

Table 1. (Continued)

	NO. OF PATIENTS (AGE); DISEASE DURATION	SYSTEMIC SYMPTOM, VISCERAL INVOLVEMENT, COMORBIDITY	BLOOD COUNTS	BONE MARROW BIOPSY	LIVER BIOPSY	TRANSAMINASE	COAGULATION	KIDNEY DISFUNCTION	TREATMENT	OUT COME
Hojo et al.[23]	1 m (73 y); 9 months	Fever	Anemia	3.4% blasts. Several erythroid cells with two nuclei, neutrophils with Pelger-Hüet–like nuclei or without granules, and megakaryocytes with multisegmental nuclei or multiple nuclei (refractory anemia)	—	↑ GOT, ↑ GPT and ↑ γGT	—	Renal failure (creatinine 2,7 mg/dL)	Prednisolone at 40 mg/d with tapering	Remission of anemia, liver and kidney disfunction
Amarapurk-ar et al.[4]	1 f (47 y); 19 months and half	Fever; right pleural effusion and ascites. Psoriasis	Normal	—	Diffuse fatty change with mild inflammation. Laparoscopy: multiple areas of fat necrosis.	↑ GOT, ↑ GPT, ↑ LDH	Normal	Normal	Prednisolone (30 mg/d) and MMF (500 mg twice a d)	Remission
Miranda-Bautista et al.[9]	1 f (42 y), 24 months	Right exophthalmos, due to a significant enhancement of the soft tissue in the right orbit. Ileocolonic involvement	Pancytopenia	—	—	Normal	Normal	Normal	IFX (5 mg/kg, repeated at wk 2, 6 and then every 8 wk)	Remission
Hagag et al.[24]	1 m (2 y and 9 months) (14 months)	Fever, hepatosplenomegaly	Microcytic hypochromic anemia	—	—	Normal	Normal	Normal	Corticosteroid treatment (2 mg/kg/d for 3 wk) and CsA (5 mg/kg/d) for 6 months.	Complete remission

Abbreviations: AZA, azathioprine; CsA, cyclosporine A; d, day; f, female; FBG, fibrinogen; FDP, fibrin degradation products; IFX, infliximab; KPTT, kaolin partial thromboplastin time; LDH, lactate dehydrogenase; m, male; MMF, mycophenolate mofetil, MTX, methotrexate; PT, prothrombin time; TT, plasma thrombo-test (or thrombin time); wk, weeks.

cell infiltration, including plasma cells, piecemeal necrosis, bile duct proliferation (in some cases with disruption of the limiting plate),[3] and edema as well as fibrosis around the bile ducts have been observed in lever biopsy.[1,3,6,11] The evolution in centrilobular pericellular fibrosis is sporadically described.[6] Suggestive signs of vasculitis, due to the presence of the thickening and cell infiltration of branches of the hepatic artery suggestive of vasculitis, were also found.[11] The liver failure, until 1980, was among the main causes of death in systemic PWCD.[3,19]

Hematological Manifestation

The clinical features of hematological involvement are anemia[1,5,19,23,32] (mostly hypochromic and microcytic,[3,14,24] occasionally normochromic and microcytic)[16], leucopenia[3,6,20] (with mainly neutropenia),[19] and thrombocytopenia.[5,11] Pancytopenia is rarely described.[9,16,17]

The findings of bone marrow aspirate varied from considerable retardation of the maturity of granulocytic series,[1] to refractory anemia, characterized by several erythroid cells with two nuclei, neutrophils with Pelger-Hüet–like nuclei or without granules, and megakaryocytes with multisegmental nuclei or multiple nuclei.[23]

The myelodysplastic syndrome (MDS) in PWCD is rarely reported.[23,33-35]

Kidney Involvement

Kidney involvement is rarely described in PWCD. The proteinuria is the most common clinical signs encountered in PWCD.[1,11,13,17] It is described, at immunochemistry, as the presence of granular immune deposits, containing IgG and IgM, on the epithelial side of the glomerular basement membrane, consistent with membranous glomerulonephritis.[13] In another case, the proliferative glomerulonephritis with glomerular lobulation and partial double track of the glomerular basement membrane was evidenced by electron microscopy and marked coarse granular deposition of IgG and IgM and slight deposition of IgA and C3 along the glomerular capillary walls were observed by the direct immunofluorescence technique.[11]

Coagulopathy

The hypofibrinogenemia, the reduction of factor XIII, factor V levels and plasminogen levels, the increase in fibrin degradation products (FDP), decreased activity of factors II, V and VIII, prolongation of the kaolin partial thromboplastin time (KPTT), prothrombin time (PT) and thrombin time (TT) are observed.[16,17,19]

Many reports describe the tendency to hemorrhagic complications, consisting of internal organ bleeding and disseminated intravascular coagulation (DIC) in the PWCD patients, but the mechanism which might cause the development of consumption coagulopathy is still unknown.[16,17,19] The possible role of the dysregulation of lipid metabolism, the destruction of the tissues and vascular wall eventually liberate tissue thromboplastin into the circulating blood, as well as active blood contact factors were taking into account.[17] In addition, abnormalities in the micro-circulation, hypofunction of the reticuloendothelial system, and disfunction of the fibrinolytic system may also take part in the pathogenetic mechanism.[17]

It is evidenced that the presence of thrombocytopenia and liver abnormalities could contribute to hemorrhagic diathesis in patients with PWCD.

Organ bleeding has been for several years the cause of death in many patients with PWCD.[1,11,16]

Miscellaneous

Perivisceral fat involvement in pericardium, pleura, omentum, and mesentery is described.[2] Abdominal involvement can include retroperitoneal panniculitis,[22,36,37] nodular mesenteritis or retractile mesenteritis,[8,38,39] and sterile splenic abscesses.[40] Mesenteric panniculitis could be present as intestinal obstruction, abdominal fullness, and tenderness[41] or abdominal and pelvic mass.[2] A case of PWCD ileocolonic involvement with histologic findings of lobular lympho-histiocytic panniculitis lipophagic granulomas and a deep cecal ulcer surrounded by thrombosed vessels was reported.[9] A macroscopic picture similar to Crohn's disease with thickening of cecal and terminal ileum wall, a large cecal ulcer covered with fibrin and nodular, hyperemic and friable margins; ileocecal valve inflammation and stenosis is described.

Mediastinitis, pleuritis, and pleural effusion are rarely described.[10,15,42] Multiple lung nodules associated to PWCD with histological examination characterized by infiltration of foam cells in the alveolar spaces and lymphocytes in endobronchitis have been observed.[43]

Bone osteolytic lesions are also noted.[21]

Treatment Choices

Effective therapeutic strategies to treat the systemic PWCD have not been identified yet and no data exist comparing the effectiveness of a therapy over another.

High doses of steroids had represented, for several years, the only treatment option.[1,5,16,17,18,19] In the three last decades, the introduction of immunosuppressive agents permitted to spare the steroid dose and to obtain complete clinical remission.

Azathioprine (AZA), a purine analogue, whose metabolites inhibit nucleotide conversions and de novo purine synthesis, impeding the DNA, RNA, and protein synthesis, has been used as first immunosuppressive agent in PWCD, by Hotta et al in 1981. At high dose, AZA is effective in skin, hematological and liver manifestation of PWCD.[6,20] However, it is described that AZA failed to reach complete remission in 2 cases.[24,37]

Cyclophosphamide (CyC), a synthetic alkylating agent, which metabolite forms irreversible DNA interstrand and intrastrand crosslinks, leading to cell apoptosis.[21] Kirch et al[21]

used CyC (200 mg/daily) in a patient with hematological and liver involvement and glomerulonephritis, describing a treatment discontinuation due to the occurrence of leucopenia and thrombocytopenia. Martin et al. used CyC (75 mg/day) in a 40-year-old patient with nodular lesions. They observed an improvement of skin lesion but the appearance of colitis induced a temporary discontinuation of CyC.[44]

Cyclosporine A (CsA) is able to block the transcription of cytokine genes in activated T cells. Hagag and Barakat[24] reported a good efficacy of CsA (5 mg/kg/die for 6 months) in a child with hematological and hepatosplenomegaly. CsA (5 mg/Kg/day) had been used with success in an 8-year-old boy with skin lesion and small vessels vasculitis.[45] Of note, CsA is, also, proved to be very effective in cytophagic histiocytic panniculitis (CHP), considered a severe variant of PWCD. It is characterized by lobular panniculitis with T helper cells infiltrated, and histiocytes containing blood cell fragments, and by severe systemic features with multiorgan failure, hypertriglyceridemia, and coagulopathy, which may lead to death.[45,46]

MMF is the 2-morpholinoethyl ester of mycophenolic acid (MPA). After assumption, it is rapidly hydrolyzed to its active metabolite, MPA. MPA potently, selectively, and reversibly inhibits inosine monophosphate dehydrogenase, interfering in the de novo pathway of purine synthesis and finally in lymphocytes activity.[47] MMF has been first approved for the treatment of acute renal graft rejection in transplant patients and then widely used as immunosuppressive agent in various autoimmune and inflammatory disorders.[47] Enk and Knop[22] first described the efficacy of MMF (2 g/day), in addition to prednisolone, in 3 patients with WDC with skin and retroperitoneal lesions, after failure of AZA and methotrexate. Başkan et al[14] reported rapid and good therapeutic response to MMF in a patient with PWCD with skin lesions, fever, systemic symptom, anemia, and arthritis. In our case, the presence of slight systemic arterial hypertension led to choose treatment with MMF rather than CsA.

Methotrexate (50 mg/daily) and hydroxychloroquine (400 mg daily) seem to not be valid treatment options in PWCD.[22,21]

With regard biotechnological drugs, few data are available. Infliximab good response is described in a patient with subcutaneous lobular panniculitis,[48] in a PWCD patient with sclerosing mesenteritis,[49] and in a PWCD patients with orbital, mesenteric, and ileocolonic involvement.[9] In a PWCD patient with subcutaneous and orbital panniculitis, a long-term good response to adalimumab, after a dramatic response to infliximab discontinued for hypersensitivity, was reported.[50] It is evidenced that TNFα is produced by T-cells and TNFα-high affinity receptors are prevalently expressed by adipose tissue, liver, muscle, gut, and kidney. T-cells seem to be involved in the early stage of PWCD, so could be reasonable to use anti-TNFα drugs to treat it. No scientific evidences are available on the use of others biotechnological drugs (rituximab, abatacept, and tocilizumab) in PWCD patients.

Conclusion

The etiology of PWCD remains unknown and the PWCD diagnosis is possible just after the exclusion of all known causes. Until 3 decade ago, the systemic involvement of PWCD was life-threatening. Liver failure and organs bleeding were the main causes of death. Recently, the published evidences of successful treatment with immunosuppressive agents are growing. As a result, a pathogenetic role of immunologically mediated reaction to diverse antigenic stimuli and T-cell dysregulation hypothesized. It is also possible that rapid, aggressive institution of immunosuppression might avoid irreversible organ injury if diagnosis is prompt. The use of CsA and MMF seems to be safe and effective compared with other immunosuppressive drugs, in a wide spectrum of PWCD systemic manifestations. Further study would be necessary to establish the usefulness of biotechnological drugs in PWCD.

Author Contributions

Rotondo C and Corrado A treated the patient, wrote and revised the paper; Mansueto N and Cici D collected the data; Corsi F and Pennella A supervised for the description of pathology; Cantatore FP made the decision of the treatement for the patient.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Patient's Consent

Written informed consent was obtained from the patient for publication of this case report.

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