Case Report

Understanding the PPP Syndrome: A Rare Combination of Pancreatitis, Panniculitis, and Polyarthritis

Amin Bagheri-Ghalehsalimi[1], Mohammad Jafari[1], Amir Aria[2], Athar Kouchak[3], Mahnaz Momenzadeh[3]

[1]Isfahan Gastroenterology and Hepatology Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Department of Internal Medicine, Alzahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Department of Clinical Pharmacy and Pharmacy Practice, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Pancreatitis, panniculitis, and polyarthritis (PPP) syndrome is a rare but serious disease that can be deadly. Its symptoms come on suddenly and unexpectedly. This disease is identified by erythematous bullous skin lesions and arthritis caused by pancreatic dysfunction. A 25-year-old man had an abdominal trauma with no past medical history. A CT scan showed pancreatic inflammation, peripancreatic edema, and mild fluid in the head of the pancreas without any collection and collection of blood in the retroperitoneum. The patient came back to the hospital 2 weeks later with a fever, abdominal pain, tender joints, redness, warmth in arms and legs, and rash on the skin. In addition, their amylase and lipase levels were increased. Based on the symptoms, the patient was referred to a rheumatologist and diagnosed with PPP syndrome with concomitant pancreatitis, panniculitis, and polyarthritis. Despite being prescribed corticosteroids and broad-spectrum antibiotics, the patient passed away. The exact pathophysiology of the additional abdominal symptoms has not yet been determined. However, some researchers have suggested that this disorder may be due to the entry of pancreatic lipase enzymes into the bloodstream. Pancreatic enzymes damage adipose tissue in the lower extremities and cause panniculitis (subcutaneous adipose tissue inflammation). The symptoms of arthritis may vary depending on the clinical case as different joints are affected and the number and symmetry of joints involved may differ. Therefore, PPP syndrome is sporadic and not easily diagnosed.

Keywords: Case report, pancreatitis, pancreatitis, panniculitis, panniculitis, polyarthritis, polyarthritis syndrome, PPP syndrome

Address for correspondence: Dr. Mahnaz Momenzadeh, Department of Clinical Pharmacy and Pharmacy Practice, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: Mahnazmomenzadehf@gmail.com
Submitted: 14-Jul-2024; **Revised:** 22-Oct-2024; **Accepted:** 26-Oct-2024; **Published:** 28-Feb-2025

Introduction

Pancreatic panniculitis is a rare skin condition caused by fat tissue damage. It affects only 0.3%–3% of patients with different pancreatic problems. Up to 40% of pancreatic panniculitis cases start with skin issues, coming before any stomach symptoms by as much as 17 months.[1] Clinically, patients show painful, tender, poorly defined, red to purplish rash that may develop ulcers and release an oily brown, thick substance due to the breakdown of fat cells known as liquefaction necrosis. Usually, these sores show up on the legs, but they can also appear on the buttocks, chest, arms, and scalp. Fat necrosis can affect not only the skin but also the fat around joints, as well as abdominal and intramedullary adipose tissue. The trio of pancreatitis, panniculitis, and polyarthritis collectively constitute the pancreatitis, panniculitis, and polyarthritis (PPP) syndrome.[2]

Berner first described this triad in 1908,[3] and since then, fewer than 70 cases have been reported in all the literature up to now.[4]

This syndrome is rare. It causes red rash on the skin, joint pain, and necrosis of fat cells inside the bones. It happens when someone has pancreatic problems, either short-term or long-term. The exact cause of this condition is not clear, but

Access this article online

Quick Response Code:

Website: www.advbiores.net

DOI: 10.4103/abr.abr_324_24

How to cite this article: Bagheri-Ghalehsalimi A, Jafari M, Aria A, Kouchak A, Momenzadeh M. Understanding the PPP syndrome: A rare combination of pancreatitis, panniculitis, and polyarthritis. Adv Biomed Res 2025;14:14.

it seems elevated levels of certain enzymes and free radicals in the blood might be responsible for the lesions.[5] While there is not much info about PPP syndrome, spotting its key symptoms early is vital. This is because the condition can lead to severe bone problems and permanent joint damage quickly, making it a serious threat to health.[6] Presented herein is the case of a man afflicted with this rare syndrome, underscoring the importance of early diagnosis crucial for the prognosis of this generally fatal clinical association due to its rarity.

Case Report

A 25-year-old man with no medical history was taken to the hospital on April 1 after a car accident and abdominal trauma. For this reason, he was referred to the emergency room. At the time of the visit, the patient had complained of severe abdominal pain. The clinical symptoms of the patient were as described below: temperature = 38.2°C, pulse rate = 115 beats/min, blood pressure = 100/65 mmHg, respiratory rate = 35 breaths/min, and oxygen saturation = 80% on room air.

In the auscultation examination of the heart, s1 and s2 were heard, and there was a decrease in left lung sound and generalized tenderness of the abdomen without rib and tenderness and guarding.

Due to abdominal trauma, he was subjected to a fast ultrasound, and mild free fluid was observed in Morrison's space. In addition, due to the decrease in left lung sound, a chest radiograph was requested, and evidence of pneumothorax was seen on the right side of the lung. Taking into account abdominal pain, abdominal and pelvic CT with venous contrast was requested, and pancreatic inflammation, peripancreatic edema, and mild fluid in the head of a pancreas without any collection were seen. In addition, collection of blood in the retroperitoneum was seen.

The patient was admitted to the ICU due to respiratory distress, pneumothorax, and aspiration pneumonia. He was placed under a chest tube, and meropenem 1 g every 8 h was prescribed for him. During hospitalization, the general condition of the patient improved, the oral diet was started, and the chest tube was removed. He was discharged from the hospital despite mild pain and an outpatient visit to a gastroenterologist with levofloxacin and metronidazole treatment. Unfortunately, the patient did not see a gastroenterologist.

Two weeks after leaving the hospital, he suffered from fever and pain, swelling, redness, and warmth of his joints.

Because of these manifestations, he was seen by a rheumatologist, who ordered rheumatologic lab tests (ANA, Anti-dsDNA, Anti-CCP, SPEP, RF, ESR, CRP, p-ANCA, and c-ANCA). Amylase and lipase samples were sent due to abdominal pain, and treatment was started with 50 mg indomethacin three times a day and 10 mg prednisolone daily. All rheumatology tests mentioned above were in the normal range, except for ESR and CRP (ESR = 105 mm/h, CRP = 92 mg/dL).

Despite treatment and given migratory arthritis in the knees and ankles, lesions resembling erythema nodosum (panniculitis), and elevated amylase and lipase, he was admitted to the hospital.

During admission, his vital signs were as follows: temperature = 38.8°C, pulse rate = 110 beats/min, blood pressure = 110/75 mmHg, respiratory rate = 18 breaths/min, and oxygen saturation = 95% on room air. Heart sounds S1 and S2 were within normal limits, and auscultation of the lungs revealed clear sounds.

Muscle strength and tone of all extremities were normal on examination.

Abdominal examination showed epigastric tenderness and tympanic on percussion. Due to epigastric tenderness and tympanic percussion, we decided to do an abdominal pelvic CT scan. CT scan showed that the head and tail of the pancreas were prominent; in addition, moderate fluid collection was detected anterior and posterior to the pancreas, probably due to previous pancreatitis [Figure 1].

CT scan showed the enlargement fluid collection (red arrow), with extension to the proximal portal vein, secondary to previous pancreatic trauma or portal vein trauma (blue arrow).

Non-blanching purpuric lesions and hyperpigmentation were seen on the medial and proximal parts of both arms. The upper extremities showed swelling of the hands and some tender joints. In addition, the lower extremities had swollen areas on both shins with superficial redness and palpable purpura [Figure 2].

The results of the patient's blood parameters are shown in Table 1.

During hospitalization, due to leukocytosis and persistent fever, infectious consultation was requested, and according to the consultation, blood culture, urine analysis, urine culture, stool exam, and stool culture were sent, which were all normal; however, considering the history of previous hospitalization and receiving antibiotics in the last 3 months, he was treated with broad-spectrum antibiotics (meropenem 1 g every 8 h and vancomycin 1 g every 12 h).

During hospitalization, he developed worsening soft tissue swelling in the extremities and aggravation of arthritis, especially in large joints. Skin lesions gradually formed

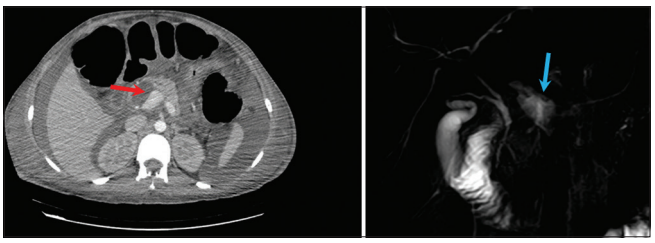

Figure 1: CT scan showed the enlargement fluid collection (red arrow) with extension to the proximal portal vein, secondary to previous pancreatic trauma or portal vein trauma (blue arrow)

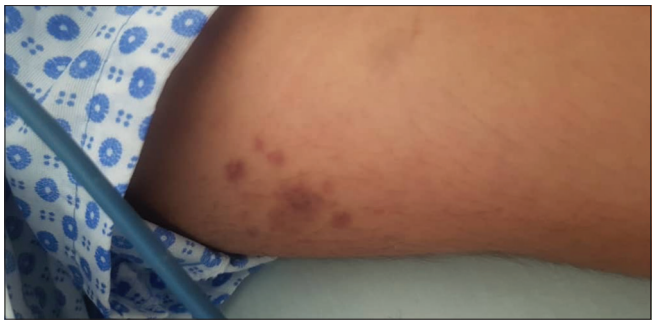

Figure 2: Erythematous cutaneous nodules and arthritic manifestations in left-hand joints

patches and ecchymosis, and some areas developed painful vesicles. In addition, he had a spiked high fever not responsive to antipyretics and antibiotics. Therefore, a rheumatology consultant was requested and PPP syndrome was diagnosed.

Hence, we started 10 mg prednisolone every 8 h for 3 days, and aspiration of fluid from the vesicles was done.

Owing to the patient's fever continued, we applied for cardiac consultation. However, there was no evidence of infective endocarditis. According to the continued severe abdominal pain and tenderness, general surgery was consulted, which recommended CT-guided percutaneous drainage of the pancreatic fluid collections, which showed albumin = 1.4 g/dL, neutrophils = 90%, white blood cell count = 4500/mm^3, and glucose = 162 mg/dL.

According to the worsening of the patient's symptoms, pulse methylprednisolone 500 mg for 3 days was started.

Ultimately, 2 days after the end of the glucocorticoid pulse, the patient experienced a decrease in oxygen saturation. Within 12 h, the patient developed ARDS and a severe reduction in SPO_2 (oxygen saturation) and thus he was intubated. Notwithstanding receiving glucocorticoid pulse and broad-spectrum antibiotics, the patient died.

Discussion

This case report shows an unusual scenario where panniculitis and clinically apparent polyarthritis develop after pancreatitis. People with either short-term or long-term pancreatitis often experience a combination of panniculitis, polyarthritis, and pancreatitis. Sometimes, pancreatitis can come with panniculitis and arthritis, which together make up PPP syndrome. Because there are not many reported cases, we are not sure about PPP syndrome yet. Each case is different in what caused it and how severe it is.[7]

Betrains *et al*.[8] (2021) looked into pancreatic diseases linked to PPP syndrome. They found that 54.2% of patients had acute pancreatitis, 30.5% had chronic pancreatitis, 11.9% had pancreatic cancer, and 3.4% had acute pancreatitis instead of chronic pancreatitis. About half of the patients had only pancreatic pseudocysts. Most of the patients were men (74.6%). The median age was 49 years, ranging from 4 to 88 years. The individual, a 25-year-old man with no notable medical background, experienced pancreatitis as a result of an abdominal trauma.

Table 1: Laboratory parameters of the patient

Parameter	Value (Normal Range)
BS	126 mg/dL (70–135)
BUN	14 mg/dL (8.8–20.5)
Cr	0.8 mg/dL (0.86–1.4)
Amylase	7770 U/L (10–100)
Lipase	6000 U/L (10–60)
WBC	1370 per microliter (4400–11000)
RBC	3.69 cells/mcL (4.5–5.9)
Hb	10.3 g/dL (14–17.5)
Hct	31.4 L/L (41.5–50.5)
Neu	82.3% (50–70)
Na^+	128 mmol/L (136–145)
LDH	889 units/L (100–480)
ESR 1h	117 mm/h (0–15)
CRP	95 mg/dL (0–10)
K	4.3 mEq/L (3.5–5.1)
Ast	46 U/L (10–40)
AlT	55 U/L (10–41)
AlP	269 U/L (100–270)

BS: Blood sugar, BUN: Blood urea nitrogen, Cr: Creatinine, RBC: Red blood cell, Hb: Hemoglobin, Hct: Hematocrit, Neu: Neutrophils, Na: Sodium, LDH: Lactate dehydrogenase, K: Potassium, WBC: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, ANA: Antinuclear antibody, anti-dsDNA: anti-double-stranded deoxyribonucleic acid, anti-CCP: anti-cyclic citrullinated peptide, SPEP: Serum protein electrophoresis, RF: Rheumatoid factor, p-ANCA: perinuclear antineutrophil cytoplasmic antibodies, c-ANCA: Antineutrophil cytoplasmic antibodies

The mortality rate of PPP syndrome has been reported up to 24%, mainly attributed to underlying pancreatic disease.[9] Our patient succumbed to the illness approximately 2 months after the diagnosis of pancreatitis. Additionally, we noted that the lipase levels in our patient (6000 units/L) were nearly 100 times higher than the average values reported in the literature, and amylase levels were also exceptionally elevated. This may indicate specific changes in the cells lining the ducts of the pancreatic cystic structure.

Pancreatitis is usually found when looking for gastrointestinal symptoms and high levels of certain enzymes in the blood. According to Chiari (1883), pancreatic panniculitis happens in about 2%–3% of people with pancreatitis. Sometimes, pancreatitis, panniculitis (inflammation of the subcutaneous tissue under the skin), and polyarthritis occur together. This is known as PPP syndrome. Mostly, pancreatic panniculitis shows up in the legs of nearly all patients, but about 25.4% might have it in their arms, and around 13.6% could have it on their trunk.[10] The patient experienced panniculitis primarily on the inner sides of their arms, particularly near the shoulders, along with noticeable redness and palpable purple discoloration in the tissue just beneath the skin of both lower legs.

Pancreatic problems can lead to panniculitis, arthritis, or bone necrosis. These conditions are twice as likely to affect men than women (2:1 ratio). A 25-year-old male got pancreatitis after an injury. Then, 2 weeks later, his upper and lower joints swelled up and got tender. This kind of thing, like our case, can happen to anyone, no matter their age.

Understanding how pancreatitis, panniculitis, and polyarthritis are related is important. Most people with this syndrome do not show the usual signs of pancreatic problems. Instead, about two-thirds have mild abdominal symptoms such as pain, nausea, or vomiting, or they might have no symptoms at all. This makes it harder for doctors to diagnose correctly and can lead to delays or mistakes in treatment. However, concerning our patient, there was severe tenderness felt in the epigastric region.

PPP mostly affects the ankles, knees, and wrists. It commonly presents as either symmetrical or asymmetrical polyarthritis, and occasionally manifests as oligoarthritis or monoarthritis. Patients have joint pain and swelling that does not get better with usual medicines such as anti-inflammatory drugs, steroids, or drugs that weaken the immune system. Our patient had severe joint pain, trouble moving around, and swollen legs that did not get better with pain medicine or corticosteroids.

People with PPP syndrome often have higher levels of lipase, amylase, or trypsin in their lab results.[9] High eosinophil levels are sometimes found together with subcutaneous fat necrosis and joint inflammation. This connection is linked to a poor prognosis and pancreatic tumors.[11] However, our patient did not have eosinophilia.

The exact cause is not fully understood. However, many researchers believe that when pancreatic enzymes enter the bloodstream, they can lead to fat tissue breakdown, especially in areas such as under the skin, bones, and joints. In most cases, high lipase levels are usually found, but other pancreatic enzymes such as amylase, phospholipase, and trypsin could also be involved. In every case, lipase levels went up a lot, but amylase did not go up in two cases. Furthermore, heightened levels of amylase alone do not suffice to induce panniculitis. In addition, even though the lipase level does not show how bad acute pancreatitis is, it seems connected to how much fat tissue is damaged outside the pancreas in PPP syndrome. Some scientists think that arthritis could be caused by fatty acids set free when certain enzymes break down fats near the joints. In our patient, both lipase and amylase levels were high: lipase at 6000 units/L and amylase at 7770 units/L.

It is hard to diagnose PPP syndrome early when joint issues or panniculitis are more noticeable than a few pancreatitis symptoms, or the other way around. Delays in finding and treating pancreatic issues can lead to more deaths. When PPP syndrome affects the bones and joints, it can cause lasting damage and make people very sick.[12]

The treatment approach varies based on the type of pancreatic injury. These treatments include the following: replacing stent in narrow pancreatic ducts, using ultrasound to guide tube placement, or removing pseudocysts with surgery or EUS + FNA.

Pancreatic diseases such as pancreatitis or cancer are very serious and can often lead to a high risk of death, just like what is happening in our case.

Panniculitis and polyarthritis are usually treated with NSAIDs and corticosteroids. Transient relief of arthritis and bone pain was noticed in this case, but generally, the response is usually mild to moderate according to most reports. There is no proof that NSAIDs and corticosteroids can make things better in the long run. They are just symptomatic treatment. About half of the patients who got better from pancreatic disease saw their skin and joint problems improve without any lasting issues. Some people got ongoing joint pain even when their pancreatic enzymes were back to normal.[13] PPP syndrome was diagnosed by considering all clinical parameters, imaging, and serological data. This rare syndrome combines panniculitis and polyarthritis, originating from pancreatitis.

Treating PPP syndrome means resolving pancreatitis and supporting care. Finding out what is causing pancreatic disease is really important so that the treatment and follow-up can be right. When someone has acute pancreatitis, it is important to start feeding them through oral nutrition as soon as possible. This helps protect their gut, keeps it from getting damaged, and stops harmful bacteria from spreading and causing more problems in the pancreas. If eating is not giving you enough calories and protein, think about getting some nutrition through a vein. Doctors need to watch out for problems that could keep pancreatic enzyme levels high.[14] Treating the pancreatitis can help with skin and joint problems. Doctors often try NSAIDs and steroids for relief, but they do not always work well. Sadly, our patient did not get better with these medicines and passed away.

Conclusion

PPP syndrome is a rare but serious condition that can lead to complications and death. Finding it early and starting treatment quickly is the key to better results. Doctors should keep PPP syndrome in mind when patients with pancreatitis also have joint pain or skin rash.

Ethics approval and consent to participate

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her clinical information to be reported in the journal. The patient understands that her name will not be published.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Rongioletti F, Caputo V. Pancreatic panniculitis. G Ital Dermatol Venereol 2013;148:419-25.
2. Narváez J, Bianchi MM, Santo P, de la Fuente D, Ríos-Rodriguez V, Bolao F, *et al.* Pancreatitis, panniculitis, and polyarthritis. Semin Arthritis Rheum 2010;39:417-23.
3. Opsmer D, Suttels V, De Keyser K. Pancreatic disease, panniculitis and polyarthritis (PPP) syndrome: A case report and review of the literature. Belg J Med Oncol 2001;5:154-8.
4. Ferri V, Ielpo B, Duran H, Diaz E, Fabra I, Caruso R, *et al.* Pancreatic disease, panniculitis, polyarthrtitis syndrome successfully treated with total pancreatectomy: Case report and literature review. Int J Surg Case Rep 2016;28:223-6.
5. Menon P, Kulshreshta R. Pancreatitis with panniculitis and arthritis: A rare association. Pediatr Surg Int 2004;20:161-2.
6. Langenhan R, Reimers N, Probst A. Osteomyelitis: A rare complication of pancreatitis and PPP-syndrome. Joint Bone Spine 2016;83:221-4.
7. Jo S, Song S. Pancreatitis, panniculitis, and polyarthritis syndrome caused by pancreatic pseudocyst: A case report. World J Clin Cases 2019;7:2808-14.
8. Betrains A, Rosseels W, Van Mieghem E, Vanderschueren S, Nijs J. Clinical characteristics, treatment, and outcome of pancreatitis, panniculitis, and polyarthritis syndrome: A case-based review. Clin Rheumatol 2021;40:1625-33.
9. Ammar H, Harrabi F, Said MA, Gupta R, Ben Ali A. Pancreatitis, panniculitis, and polyarthritis (PPP) syndrome in the setting of severe acute pancreatitis. Cureus 2023;15:e35768. doi: 10.7759/cureus.35768.
10. Pichler H, Stumpner T, Schiller D, Bischofreiter M, Ortmaier R. Pancreatitis, panniculitis and polyarthritis syndrome: A case report. World J Clin Cases 2023;11:4412-8.
11. Bernacka M, Kosztowny K, Schwartz RA, Hogendorf P, Bogaczewicz J, Woźniacka A. The pancreatitis, panniculitis, and polyarthritis (PPP) syndrome: Subcutaneous nodular fat necrosis, a cutaneous marker of pancreatic neoplasia. Acta Dermatovenerol Croat 2021;291:46-50.
12. Kim EJ, Park MS, Son HG, Oh WS, Moon KW, Park JM, *et al.* Pancreatitis, panniculitis, and polyarthritis syndrome simulating cellulitis and gouty arthritis. Korean J Gastroenterol 2019;74:175-82.
13. Dieker W, Derer J, Henzler T, Schneider A, Rückert F, Wilhelm TJ, *et al.* Pancreatitis, panniculitis and polyarthritis (PPP-) syndrome caused by post-pancreatitis pseudocyst with mesenteric fistula. Diagnosis and successful surgical treatment. Case report and review of literature. Int J Surg Case Rep 2017;31:170-5.
14. Castro JP, Atanásio G, Canelas MA, Ferreira A, Barbosa AR, Barbedo M, *et al*. A case report of pancreatitis-panniculitis-polyarthritis syndrome-An unusual but serious presentation of pancreatic disease. Scott Med J 2020;65:19-23.