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A case of pancreatitis, panniculitis and polyarthritis syndrome: Elucidating the pathophysiologic mechanisms of a rare condition



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ABSTRACT

Pancreatitis-Panniculitis-Polyarthritis (PPP) syndrome is rare and its physiopathology unclear. A 6-year old boy suffered of traumatic pancreatitis complicated by PPP syndrome. Extensive investigations demonstrated high levels of pancreatic lipase and fatty acids in the affected peripheral tissues. These findings support the sequence of peripheral lipolysis and fatty acid accumulation inducing tissue inflammation.

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1. Article

Pancreatitis-Panniculitis-Polyarthritis (PPP) syndrome is characterized by the development of erythematous cutaneous nodules typically affecting the lower extremities as well as poly- or oligoarthritis in the setting of acute or chronic pancreatitis [1]. The pathologic hallmark is fat necrosis of the affected tissues [2], but its pathophysiology has not yet been elucidated. It has been hypothesized that high circulating levels of pancreatic enzymes extravasate

into the peripheral tissue causing local lipolysis, tissue necrosis and secondary inflammation [2]. The bony or articular lesions are often mistaken for osteomyelitis or *de novo* arthritis delaying definitive treatment of the underlying pancreatitis.

2. Case report

We report a case of PPP syndrome following prolonged pancreatitis secondary to blunt abdominal trauma. Further, we have looked into its prevalence in the largest tertiary-care pediatric hospital in Canada.

A previously healthy 6-year old boy suffered a bicycle handle bar injury to the abdomen, resulting in transection of the pancreas between the head and body. He subsequently developed pancreatitis including abdominal pain and elevation of amylase (252 U/L, normal range 20–110 U/L), which increased to 1444 U/L by hospital

Abbreviations: PPP, Pancreatitis, Panniculitis and Polyarthritis; MRI, Magnetic Resonance Imaging.

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day 1, and lipase of 983 U/L (normal range 0–60 U/L). Following initial recovery with bowel rest and parenteral nutrition, he was discharged at day 9 post-injury. On day 10 he was re-admitted with abdominal pain, fever, hyperamylasemia and hyperlipasemia (peak amylase and lipase: 2362 U/L and 3807 U/L respectively). Ultrasonography imaging demonstrated the development of a pancreatic pseudocyst. The patient failed repeated attempts of advancing enteral feeding leading to the decision to perform an endoscopic retrograde cholangiopancreatography (ERCP) and an endoscopic ultrasound (EUS) to establish cyst drainage. Challenged by the needed to organize an outside adult gastroenterologist and rental of the equipment, cyst-drainage via cyst-gastrostomy was not established until 10 weeks after injury.

Five weeks following the pancreatic injury the patient developed swelling and erythema of his right index and ring fingers (Fig. 1). Subsequently his left middle finger, right great toe and his left 3rd and 5th toes showed similar lesions. Plain radiographic examination demonstrated multiple permeative lucencies in the affected phalanges, metacarpals and metatarsals with preservation of the adjacent joints (Fig. 2). Magnetic resonance imaging (MRI) of the right hand revealed multiple medullary bone infarctions with phlegmonous appearing collections in the affected areas (Fig. 3).

Rheumatologic evaluation for differential diagnosis of dactylitis was negative for anti-nuclear antibodies, rheumatoid factor and HLA B-27. The patient was treated for multifocal osteomyelitis with intravenous antibiotics.

Surgical exploration of the affected fingers of the right hand, indicated due to non-response to antibiotics, showed multiple cortical erosions with breach of the periosteum allowing the medullary canal to communicate with the subcutaneous tissues. Free cream-colored fluid was sampled from the right index (metacarpal and middle phalanx) and ring (middle phalanx) fingers for diagnostic analysis. Two fragments of the second metacarpal of the right hand were examined. Histopathology demonstrated necrotic tissue debris, which had undergone saponification, with absence of any inflammatory cellular infiltrate (Fig. 4). Microbiological cultures of the cream-colored fluid were negative for any pathogens. Extensive pathological and biochemical investigations to further look into the diagnosis and possible mechanisms of PPP revealed low levels of triglycerides (2.1 mmol) and high levels of fatty acids (10,443.5 μ M, Rando enzymatic method [3]), reflecting a lipolytic process. No amylase activity was detected (0 U/L); however the lipase activity exceeded the serum lipase by 4 times (15062.5 U/L) [4] and was further specified, using rabbit antisera against recombinant human

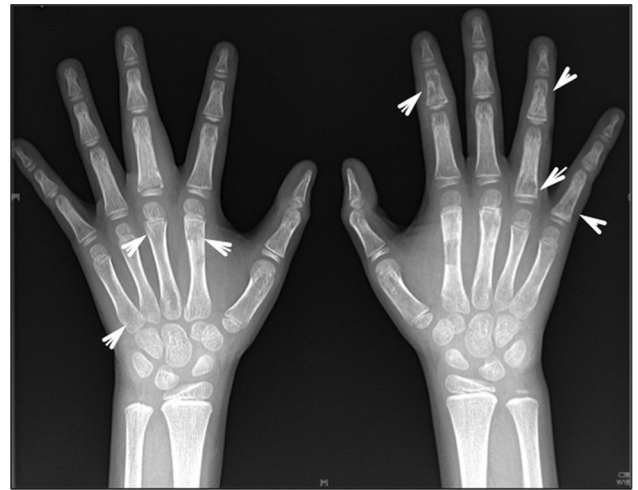


Fig. 2. X-ray shows soft tissue swelling and multiple permeative bone lucencies (arrows).

pancreatic triglyceride lipase (PTL) and recombinant human carboxyl ester lipase (CEL), as pancreas triglyceride lipase [5] (Fig. 5).

Following pancreas pseudocyst drainage at 10 weeks post injury, his abdominal symptoms resolved, his pancreatic enzymes decreased to an amylase of 138 U/L and lipase of 330 U/L and his digital lesions improved. Four months later the pseudocyst and the digital lesions had completely recovered as confirmed by serial hand x-rays, and the pancreas enzymes had normalized.

2.1. Second case identified by chart review

We performed a retrospective chart review of patients with pancreatitis seen at The Hospital for Sick Children (HSC), Toronto, between 1992 and 2012 (approved by the Research Ethics Board). We only identified one other patient of 265 children presenting with pancreatitis who had developed PPP and who was reported previously [6], yielding an incidence of 7 per 1000 pancreatitis cases. In brief, this is a 4-year old boy with progressive renal failure due to steroid refractory nephrotic syndrome and sclerosing glomerulonephritis of unknown cause, who developed acute pancreatitis (peak serum amylase 1800 U/L and lipase 1327 U/L). He was kept on bowel rest and parenteral nutrition; eight days later he developed erythematous tender nodules on his back, right flank



Fig. 1. Affected right hands of the 6-year-old boy.

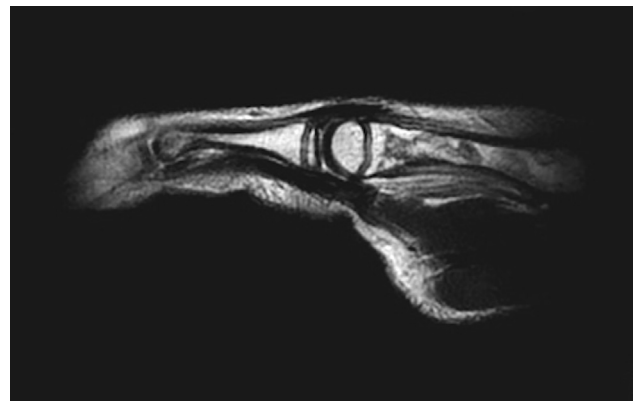


Fig. 3. MRI of the right hand showed small phlegmonous collection along the volar surface between the volar cortex and the flexor tendon and along the dorsal surface soft tissue extending over the distal interphalangeal joint.

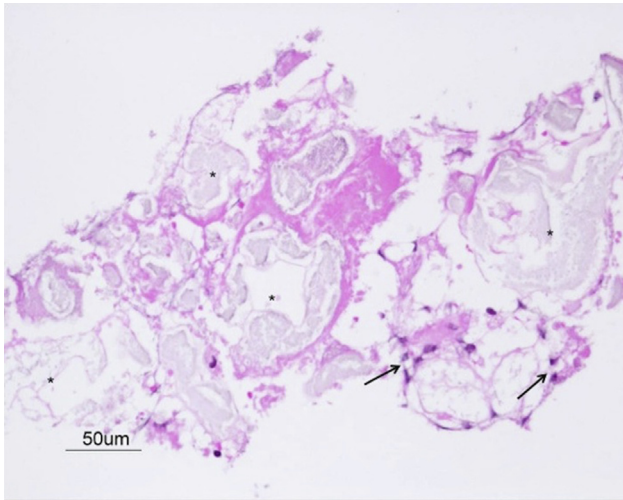


Fig. 4. Histopathology: H&E stain from right hand specimen demonstrated destroyed bone structure with saponification (asterisk) of the fatty tissue (arrows: viable adipocytes).

and knees. A biopsy of these lesions confirmed lobular panniculitis with fat necrosis and signs of saponification. The lesions resolved upon normalization of pancreatic enzymes with conservative treatment six days later.

3. Discussion

We report the case of a 6-year old boy presenting with panniculitis and intramedullary fat necrosis caused by traumatic pancreatitis. Prolonged pancreatitis due to late resolution of the pseudocyst may have caused the development of panniculitis. Nevertheless, previous reports argue against a simple linear relation between duration and magnitude of elevated pancreatic enzymes and the onset of peripheral tissue damage. Osteo-articular lesions have appeared weeks or months after the initial pancreatic event and can even predate the identification of the pancreatic disease [1,2,6].

The incidence of PPP syndrome is extremely low; a handful of pediatric cases have been published: five cases of pancreatitis with panniculitis and osteoarticular lesions and two with panniculitis

alone [6–11]. Only two patients with PPP have been identified in our hospital over the last 20 years.

The etiology of this disease entity is still unclear. The most widely accepted theory states that serum lipase extravasates into the peripheral tissues and penetrates the peri-articular space [2], thus causing lipolysis and secondary inflammation. In our patient, we detected grossly elevated concentrations of pancreatic triglyceride lipase at the site of the peripheral inflammation. Similarly, Simkin et al. described higher levels of lipase in the synovial fluid of a patient with pancreatitis and polyarthritis [12] and Forström et al. in a skin tissue specimen from a patient with panniculitis [13]. High lipase concentrations in the aspirated fluid of the peripheral lesions may not only be due to extravasation, but can either be explained by slow tissue clearance of this enzyme, or by a process that involves local production of lipase. Peripheral fat tissue expresses adipose triglyceride lipase [14] and as recently shown, also pancreatic lipases, which when activated induce fat necrosis [15]. The process observed in PPP syndrome could thus involve locally residing adipocytes, and the isolated pancreatic triglyceride lipase in the patient's fluid may stem from the patient's pancreas or his tissue adipocytes.

Interestingly, as seen in other cases, panniculitis occurred in the patient's peripheries targeting the osteoarticular space, which may indicate the higher vulnerability of this tissue. Frommer et al. recently demonstrated that fatty acids increase the production of pro-inflammatory cytokines in synovial fibroblasts and human chondrocytes in vitro [16]. The high concentration of fatty acids in the digital fluid of our patient may therefore have been sufficient to induce inflammation in this tissue.

We suggest that management of PPP-associated panniculitis and polyarthritis should mainly be directed toward evaluating and treating of the underlying pancreatitis. Our two cases indicated that resolution of the panniculitis was dependent on the resolution of the pancreatitis, which is in agreement with previous reports. Thus, clinical knowledge about the association of panniculitis and/or polyarthritis with pancreatitis is essential to avoid unnecessary investigations of the peripheral lesions, and rather direct treatment strategies toward resolution of the pancreatitis.

4. Conclusion

The pathophysiological findings in our case support earlier reports suggesting that pancreatitis induced panniculitis derive from a lipolytic process in susceptible peripheral tissues. The resulting accumulation of fatty acids in turn causes tissue inflammation and destruction. While this process is most likely initiated by extravasated lipase, exacerbation of the tissue destruction by local activated tissue adipocytes may explain the missing correlation between severity of the pancreatitis and onset of panniculitis. Clinical management should be directed toward resolution of the underlying pancreatitis.

Authors' contribution

Dr Ines Loverdos, Dr Shant Shekherdian and Dr Abdulrahman A. Al-Rasheed wrote the first draft of the manuscript and each author listed in the manuscript has seen and approved the submission of this version. Please find the authors' contribution listed below.

Study concept and design: Tanja Gonska. Acquisition of data: Ines Loverdos, Marc C. Swan, Shant Shekherdian and Abdulrahman A. Al-Rasheed.

Analysis and interpretation of data: Ines Loverdos, Tanja Gonska, Rayfel Schneider, Joel S. Fish, Bo-Yee, Khosrow Adeli PhD, Mark E. Lowe, Vijay P. Singh, Marc C. Swan, Jacob C. Langer.

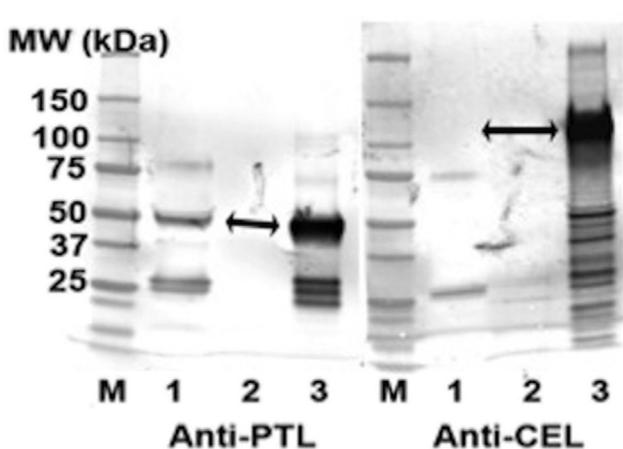


Fig. 5. Protein immunoblot of the hand fluid aspirate identified human pancreatic triglyceride lipase (PT), but not human carboxyl ester lipase (CEL). M – marker, 1 – patient sample, 2 – negative control, 3 – positive control.

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