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NECROTISING PANCREATITIS IN A PATIENT WITH CREST SYNDROME: A RARE AUTOIMMUNE GASTROINTESTINAL COMPLICATION

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ABSTRACT

Necrotising pancreatitis is a severe and life-threatening form of acute pancreatitis characterised by the necrosis of pancreatic and peripancreatic tissues due to intense inflammation and autodigestion. While the condition is uncommon, its association with autoimmune diseases such as systemic sclerosis – particularly the limited form known as CREST syndrome – is even rarer and underreported. We present a case of a 55-year-old male with a known diagnosis of CREST syndrome who was admitted with severe epigastric pain radiating to the back. Laboratory tests revealed markedly elevated lipase levels, while imaging with a CT scan showed extensive peripancreatic and retroperitoneal fluid collections consistent with necrotising pancreatitis. A thorough workup excluded common causes such as gallstones, alcohol use, hypertriglyceridemia, viral infections and drug-induced pancreatitis. Consequently, the pancreatitis was attributed to the patient's underlying autoimmune condition. The patient was managed with aggressive intravenous hydration, pain control and bowel rest, followed by gradual reintroduction of oral intake. He showed rapid clinical improvement and was discharged in a stable condition. This case underscores the importance of recognising rare gastrointestinal complications of systemic sclerosis. Vascular damage, immune dysregulation and fibrosis associated with CREST syndrome likely contributed to pancreatic ischaemia and necrosis. Clinicians should maintain a high index of suspicion for atypical presentations of pancreatitis in autoimmune patients, especially when routine aetiologies are excluded. A multidisciplinary approach is essential to ensure timely diagnosis and optimal management. This report highlights the need for increased awareness and further research into the gastrointestinal manifestations of systemic sclerosis, including its rare but significant association with necrotising pancreatitis.

KEYWORDS

CREST syndrome, necrotising pancreatitis, autoimmune pancreatitis

LEARNING POINTS

- This case illustrates an unusual overlap between CREST syndrome and necrotizing pancreatitis, a severe condition associated with high morbidity and mortality.

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INTRODUCTION

A life-threatening form of acute pancreatitis is necrotising pancreatitis (NP) whereby a portion of the pancreas undergoes necrosis, or tissue death, due to inflammation. Although it represents only 10-20% of all acute pancreatitis cases, it is associated with a high risk of complications, including multi-organ failure, infection and death[1]. It typically begins with the premature activation of pancreatic enzymes, which then triggers a destructive cascade involving immune dysregulation, vascular injury and tissue breakdown[1]. Inflammatory mediators such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and neutrophil extracellular traps amplify this response and contribute to systemic inflammatory response syndrome (SIRS), which can lead to widespread organ damage[1]. The clinical picture becomes more complex in patients with underlying autoimmune diseases such as systemic sclerosis (SSc), particularly the limited form known as CREST (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly and telangiectasia) syndrome. While gastrointestinal involvement in CREST is common, pancreatic complications are rarely reported but can significantly alter disease progression and outcomes[1]. We report a 55-year-old man with CREST syndrome who was diagnosed with NP after presenting with severe epigastric pain, highlighting a rare autoimmune-related cause of pancreatitis once common aetiologies were excluded.

CASE DESCRIPTION

A 55-year-old man with known CREST syndrome, maintained on aspirin and bosentan 62.5 mg twice daily and adherent to vascular follow-up, presented to the emergency department with severe epigastric pain radiating to the back. He reported this was his third similar episode in recent months. He is a non-smoker, does not consume alcohol, has no known drug or food allergies, and no prior surgical history. Laboratory evaluation revealed elevated lipase (1,150 U/l), with normal triglyceride levels, liver enzymes within reference range and normal serum calcium. Viral serologies were negative, excluding viral-induced pancreatitis. Abdominal ultrasound ruled out cholelithiasis. A subsequent CT scan demonstrated multiple peripancreatic and retroperitoneal fluid collections *(Fig. 1)*, consistent with complications of acute NP. After exclusion of all other common aetiologies, a diagnosis of CREST syndrome–associated NP was established. The patient received aggressive intravenous fluid resuscitation and pain control and was kept nil by mouth for 24 hours. On day 2, oral intake was resumed and by day 4, he was discharged home in a stable condition with significant symptomatic improvement.

DISCUSSION

SSc is a chronic and progressive systemic autoimmune disease involving the skin and the internal organs, characterised by a complex pathogenesis. One of the main pathogenetic pathways is the microvascular dysfunction which, associated

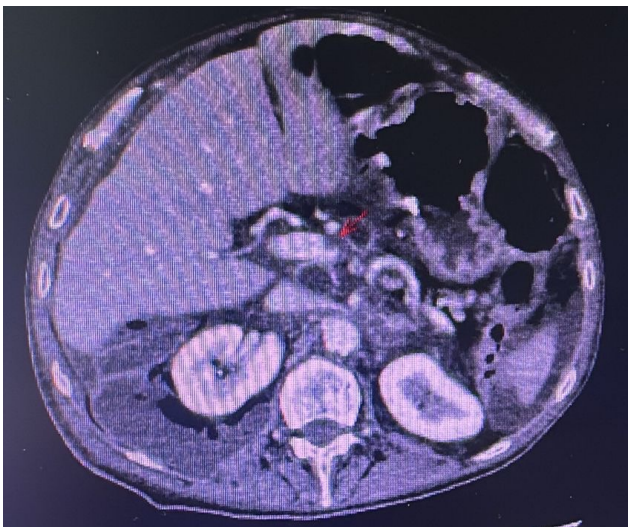


Figure 1. CT scan of the abdomen showing multiple peripancreatic and retroperitoneal fluid collections consistent with complications of acute NP (red arrow).

with an auto immune dysregulation and an uncontrolled fibroblast activation, leads to abnormal collagen production resulting in skin and organ fibrosis[2]. Several environmental factors have been implicated in the development of SSc, including silica exposure, solvent exposure, ketones and epoxy resins[3]. Additionally, evidence suggests infectious agents such as parvovirus B19, cytomegalovirus (CMV), human herpesvirus 6 (HHV-6) and Epstein-Barr virus are implicated in the pathogenesis of SSc[3].

The human leukocyte antigen (HLA) system – a major histocompatibility complex on chromosome 6 – plays a significant role in the autoimmune pathogenesis of SSc. Specific HLA class I and II alleles such as B08:01, DRB111:04, DQB1*02:02 and DPB1*13:01 are associated with SSc susceptibility across diverse ethnic groups[3]. Additional studies have implicated genetic variants involved in innate immunity (IRF5, IRF7, toll-like receptors (TLR2), T and B cell activation (CD247, TNFAIP3, STAT4, BLK) and the NF-κB pathway in SSc susceptibility[3].Treatment strategies for vascular involvement in SSc aim to improve blood flow, reduce vasospasm and prevent further vascular damage, using agents such as vasodilators, nitric oxide donors, prostaglandins, phosphodiesterase inhibitors, ACE inhibitors, SSRIs, alpha-adrenergic blockers, endothelin receptor antagonists, statins, anticoagulants, antioxidants and calcium channel blockers[4].

Vasculopathy is an early and central feature in SSc, typically presenting as Raynaud's phenomenon and potentially progressing to digital ulcers, pulmonary arterial hypertension and scleroderma renal crisis. Pathological hallmarks include endothelial cell (EC) injury, intimal proliferation, perivascular inflammation and capillary loss. EC damage is mediated by oxidative stress, infections, cytotoxic T cells and anti-endothelial cell antibodies (AECAs). This leads to apoptosis, impaired vascular integrity and a shift towards vasoconstrictors such as endothelin-1 (ET-1) and inflammatory cytokines (IL-6, IL-8, TGF-β1), with diminished

vasodilators such as nitric oxide (NO) and prostacyclin. This promotes microvascular ischaemia, platelet aggregation and vessel wall thickening via proliferation of pericytes and vascular smooth muscle cells (VSMCs) expressing platelet-derived growth factor (PDGF) receptors[3,4]. AECAs and autoantibodies against endothelin-1 type A receptor and angiotensin II type 1 receptor worsen vascular damage, while defective angiogenesis persists due to antiangiogenic factors (angiostatin, thrombospondin-1, VEGF165b) and downregulation of angiogenic regulators such as FLI1 and desmoglein-2, despite elevated VEGF, PDGF and FGF-2[3,4]. Additionally, endothelial-to-mesenchymal transition, driven by TGF-β, endothelin (ET)-1, Wnt/β-catenin and other mediators converts endothelial cells into myofibroblasts, alongside transdifferentiation of pericytes, VSMCs and adipocytic progenitors under profibrotic signals[3,4].

Immune activation further drives chronic inflammation and fibrosis. Innate immunity involves upregulated TLRs (2, 4, 8), a type I interferon (IFN-I) signature via STAT4, IRF5 and plasmacytoid dendritic cells (pDCs), and NLRP3 inflammasome activation releasing IL-1β, IL-18 and IL-33, which directly stimulate fibroblasts. Monocytes, type II macrophages, mast cells and innate lymphoid cells contribute via IL-6, MCP-1 and reactive oxygen species (ROS) [3]. Adaptive immunity features a Th2-biased T-cell response (IL-4, IL-13) promoting myofibroblast differentiation, with hyperactivated memory B cells producing autoantibodies, IL-6 and TGF-β, sustaining fibrosis [3].

Fibroblast abnormalities are central to fibrosis, marked by persistent activation, Fas/FasL-mediated apoptosis resistance and autocrine production of profibrotic mediators (connective tissue growth factor – CTGF, ROS, IL-1α, IL-6, IL-8). These cells display proteomic remodelling affecting cytoskeleton, metabolism and wound healing, with epigenetic changes such as FLI1 repression and hypermethylation of Wnt antagonists (DKK1, SFRP1) perpetuating profibrotic gene expression. Central drivers include hyperactivated TGF-β/Smad2/3, ERK (extracellular signal-regulated kinase, JNK (c-Jun N-terminal kinase) and PI3K/Akt signalling pathways, alongside overexpressed PDGF, CTGF (connective tissue growth factor), dysregulated Wnt signalling and proinflammatory cytokines (IL-6, IL-13, IL-17). Additionally, damage-associated molecular patterns such as HMGB-1 (high mobility group box 1) and S100 proteins activate TLR4-dependent profibrotic pathways, correlating with disease severity and complications such as interstitial lung disease, scleroderma renal crisis and gastrointestinal involvement[3].

Studies have shown that immunoglobulins from SSc patients impair cholinergic signalling in the gastrointestinal (GI) tract by reducing acetylcholine release and contractile responses in colonic tissue. These antibodies directly bind to M3 muscarinic receptors (M3-R) on GI smooth muscle and myenteric cholinergic neurons, inhibiting M3-R agonist-induced contractions[5]. Cell-mediated immune dysfunction in SSc is primarily driven by Th2 (T helper 2) CD4+ T cells releasing IL-4, IL-13 and TGF-β, which promote fibroblast activation and conversion into myofibroblasts, leading to excessive type I and III collagen deposition. Histological changes in the gastric wall of SSc patients include severe fibrosis, varied collagen types, abundant myofibroblasts and elevated profibrotic factors, contributing to impaired neuronal signalling, muscle contraction, autonomic dysfunction and GI dysmotility[6]. Upper GI complications are common and include laryngo-oesophageal or gastro-oesophageal reflux disease, presenting with hoarseness, oropharyngeal dysphagia, reflux and heartburn. Lower oesophageal sphincter dysfunction and oesophageal dysmotility cause distal dysphagia, while gastroparesis presents as early satiety, bloating, nausea, vomiting and unintentional weight loss[7]. Lower GI dysmotility – the hallmark of advanced disease – affects the small and large intestines and anorectal region, presenting with distension, bloating, constipation, diarrhoea and abdominal pain, often due to neuropathic and myopathic processes delaying colonic transit[7]. Liver disease in systemic sclerosis is uncommon, affecting approximately 1.5% of patients, with primary biliary cirrhosis being the most common. Other reported hepatic complications include nodular regenerative hyperplasia, idiopathic portal hypertension, spontaneous liver rupture, hepatic infarction and bile duct obstruction linked to vasculitis. Pancreatic involvement, though uncommon, may present as acute pancreatitis, painless pancreatic failure or progressive exocrine dysfunction, found in 33–61% of patients, potentially contributing to diarrhoea[6]. Fatal pancreatic infarction and acute haemorrhagic pancreatitis secondary to the occlusion of medium-sized pancreatic arteries have also been reported[5]. One case report from 1980 described a 55-year-old female with SSc who developed fatal pancreatic necrosis from extensive arteritic changes, initially presenting with hypertension and renal involvement, with the autopsy showing chronic renal fibrosis and active pancreatic vasculitis[8].

NP is an advanced and often fatal complication of acute pancreatitis. It can be characterised by necrosis of pancreatic and/or peripancreatic tissues due to extreme inflammation occurring as a result of autodigestion from prematurely activated pancreatic enzymes[1]. This condition causes local tissue damage, triggers SIRS and increases organ failure risk as well as sepsis, especially when necrosis becomes infected[9]. Patients present with severe abdominal pain, vomiting and systemic fever. NP is definitively diagnosed with contrast-enhanced CT scan, which is the gold standard for distinguishing viable from necrotic tissue and best performed after 72 hours from initial presentation for optimal demarcation[10]. Other imaging tools such as MRI and endoscopic ultrasound may add value in some cases. There is now a shift in surgical practice towards a stepwise approach emphasising less invasive techniques and better patient outcomes while minimising complications[10]. The diagnosis and severity staging of NP are guided by the Revised Atlanta Classification, which categorises the disease

based on the extent of necrosis, presence of complications and associated organ dysfunction[10]. Early management is active resuscitation of fluids, pain control, nutritional support – with enteral nutrition being preferred early on – and cautious monitoring for complications. For infected necrosis, therapy is deferred until four weeks since the onset of symptoms, once the fluid is safely contained, making drainage or necrosectomy safer through a percutaneous, endoscopic or retroperitoneal approach[9].

One case similar to ours was reported by Greif et al., in which a 43-year old man with CREST syndrome and progressive systemic sclerosis presented with a four-year history of relapsing abdominal pain – the result of chronic pancreatitis, not associated with alcoholism, biliary disease or any of the known causes of pancreatitis, suggesting a possible association between CREST syndrome and pancreatitis as in our case[11].

CONCLUSION

This case illustrates a rare overlap between CREST syndrome and NP, a severe condition associated with high morbidity and mortality. Vascular abnormalities and fibrosis from systemic sclerosis likely contributed to pancreatic ischaemia and an exaggerated inflammatory response. Management requires prompt diagnosis, supportive care and minimally invasive interventions. In autoimmune conditions such as systemic sclerosis, immune dysregulation and vascular compromise can worsen pancreatic injury and complicate recovery. The case highlights the importance of a multidisciplinary, personalised approach and the need for further research to improve outcomes in these complex patients?

REFERENCES

1. Zeng Y, Zhang JW, Yang J. Endoscopic management of infected necrotizing pancreatitis: Advancing through standardization. *World J Gastroenterol* 2025;**31**:107451. doi: 10.3748/wjg.v31.i20.107451
2. Bandini G, Bellando Randone S, Manetti M, Dagna L, Matucci Cerinic M, et al. Moggi Pignone, Endotheliopathy in systemic sclerosis: from endothelium-dependent vasodilation to the dysfunction of the vascular reserve, is the paradise lost? *Arthritis Res Ther* 2025;**27**:107. doi: 10.1186/s13075-025-03568-x
3. Son HH, Moon SJ. Pathogenesis of systemic sclerosis: an integrative review of recent advances. *J Rheum Dis* 2025;**32**:89-104. doi: 10.4078/jrd.2024.0129
4. Pattanaik D, Brown M, Postlethwaite AE. Vascular involvement in systemic sclerosis (scleroderma). *J Inflamm Res* 2011;**4**:105-25. doi: 10.2147/JIR.S18145
5. Kumar S, Singh J, Rattan S, DiMarino AJ, Cohen S, Jimenez SA. Review article: pathogenesis and clinical manifestations of gastrointestinal involvement in systemic sclerosis. *Aliment Pharmacol Ther* 2017;**45**:883-898. doi: 10.1111/apt.13963
6. McFarlane IM, Bhamra MS, Kreps A, Iqbal S, Al-Ani F, Saladini-Aponte C, et al. Gastrointestinal Manifestations of Systemic Sclerosis. *Rheumatology (Sunnyvale)* 2018;**8**:235. doi: 10.4172/2161-1149.1000235
7. Volkmann ER, McMahan Z. Gastrointestinal involvement in systemic sclerosis: pathogenesis, assessment and treatment. *Curr Opin Rheumatol* 2022;**34**:328-336. doi: 10.1097/BOR.0000000000000899
8. Abraham AA, Joos A. Pancreatic necrosis in progressive systemic sclerosis. *Ann Rheum Dis* 1980;**39**:396-398. doi: 10.1136/ard.39.4.396
9. Maatman TK, Zyromski NJ. Surgical Step-Up Approach in Management of Necrotizing Pancreatitis. *Gastroenterol Clin North Am* 2025;**54**:53-74. doi: 10.1016/j.gtc.2024.10.001
10. Rainho A, Sridharan M, Strand DS. Pancreatic necrosis: a scoping review. *Minerva Gastroenterol (Torino)* 2025;**71**:48-64. doi: 10.23736/S2724-5985.24.03658-1
11. Greif JM, Wolff WI. Idiopathic calcific pancreatitis, CRST syndrome and progressive systemic sclerosis. *Am J Gastroenterol* 1979;**71**:177-182.