# LETTERS TO THE EDITOR

## CAID syndrome and a two year clinical outcome. A case report

**To the Editor,**

Chronic Atrial and Intestinal Dysrhythmia Syndrome (CAIDS) is a disease that affects the Cajal cells in the intestine, resulting in decreased motility and chronic pseudo-obstruction of the intestine. The onset of the disease is usually at a young age, and heart and bowel involvement are simultaneous [1].

A 31-year-old woman presented with abdominal pain, fever, and weight loss. The patient had a history of pacemaker implantation 14 years previously for sick sinus syndrome, diagnostic laparotomy and ileostomy 3 years previously, and PEG placement 2 years previously. In the analysis of the genetic sequence, a homozygous mutation in the *SGOL1* gene was documented. The patient was admitted to our hospital because of abdominal pain and weight loss. An ileostomy was performed three years ago, but the patient‘s discomfort increased after surgery, and she lost 10 kg. A central venous catheter for total parenteral nutrition (TPN) was inserted in the sixth month of our follow-up. During this period, the daily caloric intake of the patient was calculated, TPN and enteral nutrition were given. The patient was discharged with a weight of 43 kg after 30 days of nutritional support. She was hospitalized for pneumosepsis in the 18th month of our follow-up. The deep tracheal aspirate and blood culture grew Candida parapsilosis. Due to low oxygen saturation, she was electively intubated. She was extubated 10 days later. A thrombus at the tip of the pacemaker lead, consistent with septic emboli, was seen on the echocardiogram. There was no evidence of infective endocarditis or valvular regurgitation. Imaging studies (Fig. 1) revealed areas of fungal infection in the liver. Despite treatment with antibiotics and antifungals, the patient died of sepsis.

The diagnosis of CAIDS is challenging. Sinoatrial node involvement causes bradycardia in CAIDS, while Cajal cell involvement causes intestinal pseudo-obstruction [1, 2]. In our case, an ileostomy was performed but after the operation, the patient experienced increased discomfort and a loss of about 10 kg. The literature shows that there is no benefit from surgical treatment for CAIDS [3]. The nutritional status is the most important issue, and if the patients are able to receive nutrition orally, further treatment may not be necessary. Information on the incidence, diagnosis, and treatment of CAIDS is lacking in the literature. Intestinal transplantation has been recommended in circumstances where quality of life is poor in the absence of effective treatment or in instances where complications related to parenteral nutrition are common [4]. In our case, the patient developed recurrent candidiasis, septic embolism, and evidence of fungal infection in the liver. Ultimately, the patient died as a result of these complications. Consequently, it is imperative to closely monitor CAIDS patients for septic embolism due to the implanted pacemaker electrode. It is crucial to recognize that catheter- or electrode-related septic emboli may increase mortality in these individuals without evidence of infective endocarditis.

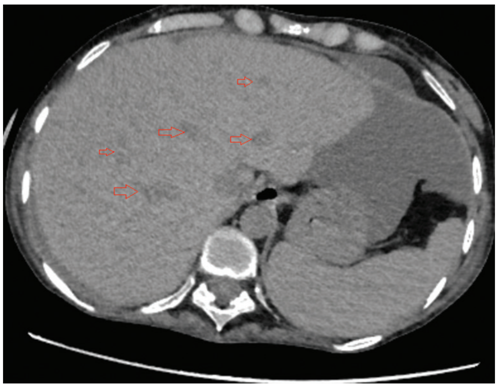

**Fig. 1**. Areas of fungal infection in the liver (red arrows).

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**Conflicts of interest:** None.

DOI: 10.15403/jgld-5772

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## Gastric perineurioma: a rare entity with different clinical presentations. A case report

**To the Editor,**

We herein report a case of gastric perineurioma found in a 77-year-old man who presented to the emergency department for severe anemia. At admission, laboratory tests revealed hemoglobin levels of 5.8 g/dL with a low mean cellular volume (MCV 60 fL). He also complained of epigastric pain and heartburn. There was no evidence of melaena or haematochezia.

Upper gastrointestinal endoscopy showed two hyperemic subcardial sessile polyps, without signs of recent bleeding (Fig.1a). After gastric polypectomy, the immunohistopathological examination showed a hyperplastic polyp of the antrum and a polyp of the gastric body with bland spindle cells incorporating reactive glandular elements with positivity for epithelial membrane antigen (EMA), glucose transporter-1 (GLUT1) and CD34, without cytologic atypia or mitotic activity (Fig. 1). Overall, the immune-morphological features suggested a diagnosis of gastric perineurioma. Colonoscopy and video capsule endoscopy additionally excluded other actively bleeding lesions. Further imaging including chest X-ray and abdominal ultrasound excluded the presence of metastatic lesions, in line with the benign histopathological features of the polyps. During hospitalization hemoglobin stability was ascertained and allowed a safe discharge. At planned follow-up, laboratory tests confirmed hemoglobin levels of 13.7 g/dL.

To our knowledge, this is the seventh case of gastric perineurioma.

Perineuriomas are soft tissue neoplasms composed of cells resembling normal perineurium [1]. They have been divided in 2 categories according to their localization: those with intraneural localization and a more common extraneural soft tissue group [1]. Although they have benign characteristics, sporadic cases of malignant perineuriomas have been reported; in particular, approximately 5% of the cases may present local recurrence, while no metastases have been recorded in the literature [1]. The diagnosis is based on histology and immunohistochemistry. These tumors are hypercellular and composed of homogeneous spindle cells; they are composed of elongated curved or wrinkled cells, their nuclei are elongated, spindle-shaped and have a wavy profile and long, bipolar eosinophilic processes [1, 3]. Typically, perineuriomas feature

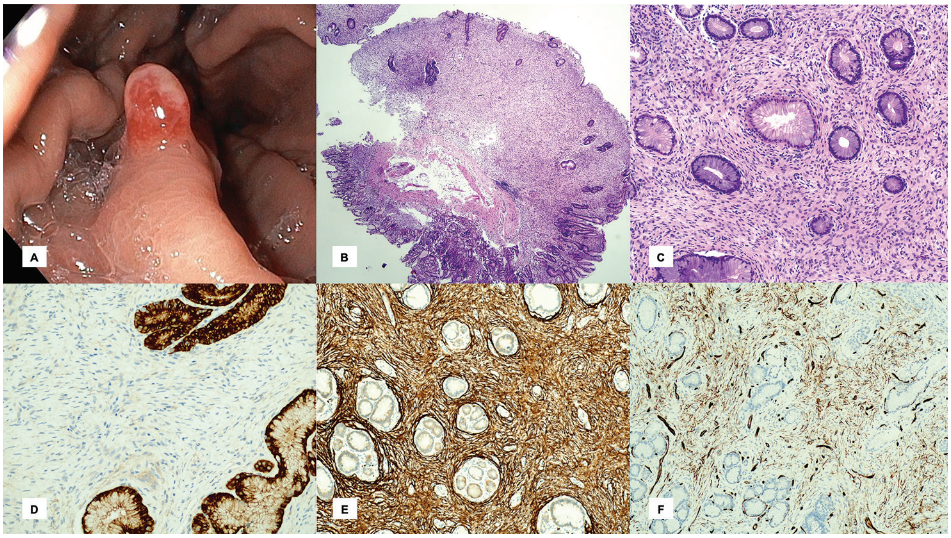


**Fig. 1.** Panel A) Endoscopic features of gastric perineurioma; B) Histological examination revealed a poorly circumscribed proliferation of bland spindle cells, confined to the lamina propria of the gastric mucosa. The muscularis mucosae appeared slightly disorganised. The lamina propria was expanded with entrapped gastric glands, some of which showed hyperplastic architecture. The surface epithelium was denuded but there was no ulceration (haematoxylin & eosin, magnification 2x); C) Cytologically, the bland-looking cells showed pale, eosinophilic cytoplasm, indistinct cell borders and ovoid to spindled nuclei with inconspicuous nucleoli. There was no cytological atypia, necrosis, or mitosis. (Haematoxylin & Eosin, magnification 4x); D) Staining for epithelial membrane antigen (EMA) featured weak staining in the long cytoplasmic processes of spindle cell component compared to the strong staining of gastric glands (magnification 20x). E) Glucose transporter-1 (GLUT1) showed diffuse and strong positive staining (magnification 20x). F) Spindle cells were also focally and weakly positive for CD34 (magnification 20x). Immunohistochemical stains for S100, smooth muscle actin (SMA), CKIT and MUC4 were negative.

weak expression of EMA (epithelial membrane antigen), and diffuse staining for GLUT-1 (glucose transporter-1), and claudin-1; they are negative for S-100 protein, CD117/KIT and neurofilaments [1]. Intestinal perineuriomas often present in the colon as small sessile polyps detected during colonoscopy.

There are very few data on gastric perineuriomas, 6 cases being previously described [2-7]. They seem to appear more commonly in women (female/male ratio 5:2) and in different ages (between 25 and 77 years old) [2-7].

The reported patients had many different clinical presentations including epigastric pain, reflux-type symptoms, dyspepsia, nausea, vomiting, recurrent upper gastrointestinal bleeding and anemia, solid food dysphagia. All the above symptoms were reported to be relieved after the tumor removal [2, 3, 5-7]. Only one out of six were diagnosed during screening endoscopy in asymptomatic individuals [4].

The most common endoscopic presentations are represented by either polyps, or bleeding gastric masses, most commonly in the gastric body [2-7]. Histologically, the tumors were represented by bland spindle cells proliferation composed of cells with wavy nuclei and positive for EMA, GLUT-1 and claudin-1, and negative for S-100 protein and neurofilaments [2-7].

In conclusion, gastric perineurioma is a very rare entity. Further studies are required to give a better comprehension of their natural history, the actual relationship between clinical presentation and endoscopic findings and their impact on one's prognosis.

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**Conflicts of interest:** None.
DOI: 10.15403/jgld-5829

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## Childlessness in patients with inflammatory bowel disease – comments on Swiss experience

**To the Editor,**

We commend Sulz et al. [1] for their meticulous study titled "Childlessness in Patients with Inflammatory Bowel Disease – Data from the Prospective Multi-center Swiss IBD Cohort Study" published in *Journal of Gastrointestinal and Liver Diseases*. This study delves into the prevalence of childlessness and infertility among individuals with inflammatory bowel disease (IBD). Notably, the study reveals a higher rate of childlessness in females with Crohn's disease (CD) compared to the general Swiss population, while the rate remains similar in women with ulcerative colitis (UC). These findings underscore the significance of addressing this aspect in IBD management and emphasize the need for further research in this domain.

However, there were few aspects needed to be addressed, such as, the study did not specifically mention the robust associations observed between mental–behavioral disorders (particularly in men), congenital anomalies, and endocrine–nutritional–metabolic disorders (most notably in women). Additionally, novel associations were identified for inflammatory and autoimmune diseases. These findings offer valuable insights into the complex relationship between diseases and involuntary childlessness [2].

Women with IBD often choose not to have children due to concerns about the impact of IBD on pregnancy and potential inheritance of the disease as well as psychological burden. However, addressing patient knowledge gaps and providing accurate information can help reduce unnecessary childlessness. Further research and targeted interventions are essential to support family planning decisions in IBD patients [3].

Male infertility in male IBD was commented on, however an important inclusion of female early pregnancy loss due to male IBD wasn‘t commented on. As emerging evidence suggests that female partners of men with Crohn's disease may face an elevated risk of experiencing early pregnancy loss. This intriguing observation needed to be considered by the article as it underscores the need for further investigation into the complex interplay between male health conditions and reproductive outcomes [4].

The article mentioned a 2023 meta-analysis which concluded that (IBD) might reduce ovarian reserve, potentially impacting fertility. However, a more recent study from May 2024, focusing on Crohn's disease (CD) patients, did not find a significant decrease in ovarian reserve. As medical professionals, we should consider both studies and stay informed about evolving research [5].

The article also highlights the lack of understanding among patients with inflammatory bowel disease (IBD) regarding fertility and pregnancy outcomes. Patients' misconceptions may contribute to voluntary childlessness

(VC). Overestimation of risks related to IBD heritability, congenital abnormalities, and medication teratogenicity can lead to unnecessary childlessness. Accurate counselling addressing fertility and pregnancy outcomes is crucial, and patient education programs could correct misconceptions. The decision to remain childless results from an elaborate mesh of disease burden, knowledge gaps, and patient attitudes. Gastroenterologists should actively address fertility concerns during preconception counseling to empower informed decision-making. The article [1] contributes greatly to an important aspect of treatment modality which is often an overlooked therapeutic option. Monitoring this valuable study cohort to evaluate long-term results would be intriguing and a valuable addition to the literature.

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**Conflicts of interest:** None.
DOI: 10.15403/jgld-5830

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## Idiosyncratic acute liver failure induced by Tirzepatide

**To the Editor,**

A 33-year-old 63 kg female was admitted with a 3-week history of acute vomiting associated with chest and abdominal pain. The vomiting episode started shortly after a 5 mg dose change (5 to 10 mg) of tirzepatide, a novel dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist licensed for weight loss. She had sourced it privately from an online pharmacy and been taking the medication weekly subcutaneously for 4.5 months, cumulating in 25 kg of weight reduction. On admission, she was profoundly hypokalaemic (K: 2.5 mmol/L), hyponatraemic (Na: 128 mmol/L) and clinically dehydrated. Her vital signs were within normal ranges. A computed tomography (CT) chest and abdomen demonstrated a pneumomediastinum with ascending emphysema to the neck, in keeping with an oesophageal perforation. She was admitted to intensive care for central potassium replacement and started on intravenous piperacillin-tazobactam and fluconazole as prophylactic cover.

On day 2 of her admission, it was noted that her alanine transaminase (ALT) had risen from 13 to 695 (IU/L), and her international normalised ratio (INR) deranged at 5.7 (no previous results to compare), with relatively normal bilirubin 19 (μmol/L). Prior to this, she had received two doses of antibiotics and single dose of fluconazole. As she was physiologically stable, her oesophageal perforation was managed conservatively. A full liver screen was undertaken, including viral and autoimmune testing, all of which were normal/negative. Supportive liver care with intravenous N-acetyl-cysteine and vitamin K injections was initiated. Despite this, her liver function continued to deteriorate (Table I) and clinical examination revealed generalised tenderness to the abdomen, in particular at the liver edge, with no signs of encephalopathy. A CT liver triple phase demonstrated features in keeping with acute hepatitis and diffuse parenchymal injury. Roussel Uclaf causality assessment (RUCAM) of drug-induced liver injury (DILI) determined an R ratio >5 indicating hepatocellular injury along with a 'possible' causality assessment for tirzepatide causing the liver failure. Fortunately, five days after the acute deterioration, liver function began to improve (Fig. 1), and she was discharged 10 days after admission. Liver function had returned to normal 2 weeks after discharge.

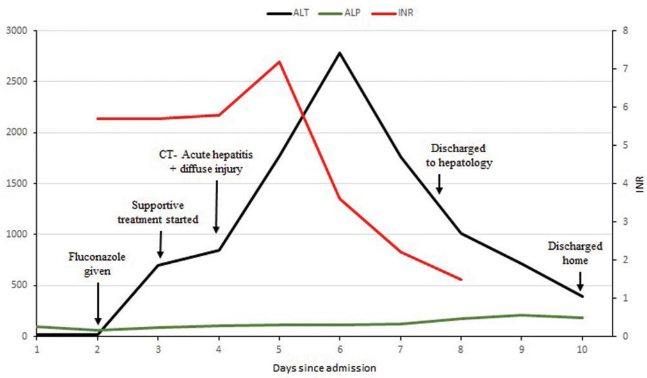


**Fig. 1.** Alanine transaminase (ALT), alkaline phosphatase (ALP) and international normalised ratio (INR) values during hospitalisation.

In this case, an increase in the dose of tirzepatide was strongly associated with an acute liver injury. There have been three case reports [1-3] of tirzepatide causing acute liver failure in different circumstances. Of those, only one occurred as an acute event with suggested toxicity after a dosage change [1]. In our case, the patient was exhibiting signs of tirzepatide toxicity with prolonged vomiting on admission, having taken the medication in accordance with prescribed dosages. Notably, the tirzepatide

**Table I**. Blood test during hospitalisation

| Test | Unit | Normal range | Day 0 | Day 2 (AM) | Day 2 (PM) | Day 3 | Day 5 | Day 6 | Day 8 | Day 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| ALT | U/L | 0-34 | 13 | 13 | 695 | 845 | 1767 | 2783 | 1012 | 393 |
| ALP | U/L | 30-130 | 92 | 64 | 106 | 105 | 115 | 115 | 173 | 185 |
| Bilirubin | µmol/L | 0-20 | 10 | 8 | 19 | 50 | 40 | 58 | 56 | 79 |
| INR | | 0.8-1.2 | n/a | n/a | 5.7 | 5.8 | 7.1 | 3.6 | 1.5 | n/a |
| AST | U/L | 0-34 | n/a | n/a | n/a | 2619 | 4834 | n/a | n/a | n/a |
| Ammonia | µmol/L | 15-40 | n/a | n/a | n/a | n/a | 74 | n/a | 57 | n/a |
| GGT | U/L | 0-37 | n/a | n/a | n/a | 110 | n/a | n/a | n/a | 384 |
| Albumin | g/L | 35-50 | 42 | 27 | 29 | 29 | 27 | 29 | 30 | 27 |
| Hb | g/L | 120-150 | 154 | 116 | 126 | 120 | 102 | 78 | 82 | 80 |
| WCC | $10^{*9}$/L | 4.0-10.0 | 15.9 | 4.2 | 9.8 | 8.5 | 7.8 | 5.2 | 5.8 | 6.4 |
| Platelet | $10^{*9}$/L | 150-410 | 307 | 148 | 236 | 195 | 112 | 72 | 76 | 99 |
| Creatinine | µmol/L | 45-84 | 99 | 47 | 40 | 42 | 53 | 49 | 48 | 26 |
| Glucose | mmol/L | 4.0-8.0 | 5.8 | 6.0 | 5.8 | 5.8 | 6.1 | 7.2 | 7.0 | n/a |
| pH | | 7.35-7.45 | 7.43 | 7.44 | 7.44 | 7.45 | 7.44 | 7.42 | n/a | n/a |
| Lactate | mmol/L | 0.5-2.0 | 5.3 | 5.4 | 5.4 | 2.7 | 2.0 | 1.4 | n/a | n/a |

ALT: alanine transaminase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; INR: international normalised ratio; GGT: gamma glutamyl transpeptidase; Hb: hemoglobin; WBC: white blood cells; n/a= not available.

dose change was contrary to recommendations in the British National Formulary which advises increases of 2.5 mg at four weekly intervals. We suggest that her rapid weight loss, acute dehydration and malnutrition reduced her functional liver reserve leading to tirzepatide-induced liver injury. There are several proposed mechanisms to which tirzepatide could cause DILI however; no formal study has confirmed liver injury propensity. Previous laboratory testing on liver cells found no CYP isoenzyme effects of tirzepatide at a level to cause clinically relevant drug interactions or liver injury [4]. Further research is required to understand how tirzepatide impacts functional liver reserve. Secondly, the administration of a single dose of fluconazole may have caused a further hepatic insult. On the background of tirzepatide-induced liver injury, we hypothesise that this second liver insult was enough to trigger fulminant liver failure.

In conclusion, our case highlights the need for caution when prescribing medications in patients exhibiting signs of tirzepatide toxicity and suggests close monitoring of liver function in patients taking tirzepatide, particularly during dose changes. With the emergence of other cases within the past 12 months, there are ongoing concerns regarding the regulation and monitoring of private weight loss prescriptions.

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**Conflicts of interest:** None.
DOI: 10.15403/jgld-5967

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