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ASIDE Case Reports

Case Report

Noonan Syndrome and Osteoporosis: A Comprehensive Case Study and Literature Review

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ABSTRACT

Noonan syndrome (NS) is a genetic disorder caused by mutations in the RAS/MAPK signaling pathway, typically characterized by unique physical features, congenital heart defects, and short stature. Osteoporosis (OP), although uncommon in NS, can significantly impact patients' quality of life. We report the case of a 60s-year-old male with NS who experienced progressive osteoporosis over seven years. Dual-energy X-ray absorptiometry (DEXA) scans revealed a marked decline in bone mineral density (BMD) accompanied by multiple fractures. Despite normal vitamin D and parathyroid hormone intact levels, the patient's BMD continued to deteriorate, leading to vertebral compression fractures that necessitated surgical intervention. This case highlights the importance of early osteoporosis screening and prompt management in NS patients to prevent severe complications. Further research is warranted to explore the mechanisms underlying bone fragility in NS and to develop targeted therapeutic strategies.

1. Introduction

Noonan syndrome (NS) is a genetic condition that presents unique physical features and medical complications. It affects approximately 1 in 1,000 to 2,500 individuals worldwide and results from mutations in the RAS/MAPK signaling pathway, including genes like PTPN11, SOS1, RAF1, and others [1, 2]. NS arises from de novo mutations, which are not inherited from the parents, or mutations in RAS/MAPK pathway genes, with PTPN11 being the most frequently affected. This pathway regulates cell growth, differentiation, and survival, and disruptions lead to the characteristic features of NS [3].

NS often includes congenital heart defects, such as pulmonary valve stenosis, and distinctive facial traits, such as a webbed neck, hypertelorism (wide-set eyes), and low-set ears. Other frequent features include short stature, intellectual and developmental delays, gonadal dysfunction, hearing loss, and an increased cancer risk [1, 2].

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Osteoporosis weakens bones by reducing bone mass and deteriorating bone tissue, typically affecting older adults and postmenopausal women [4]. Researchers are increasingly exploring the link between NS and osteoporosis. Genetic mutations associated with NS, particularly in the PTPN11 gene, directly impact bone development and contribute to abnormal bone growth [5]Additionally, mobility limitations in individuals with NS reduce weight-bearing activity, which increases their risk of osteoporosis. This report documents a detailed case of NS associated with a decade-long progression from osteopenia to osteoporosis despite extensive treatment regimens including bisphosphonates, teriparatide, and Denosumab. It provides a detailed longitudinal follow-up through serial DEXA scans. It offers novel insights into the challenges of managing osteoporosis in NS and underscores the need for early screening and intervention research.

2. Case Presentation

A male patient in his 60s presented for evaluation and management of ongoing osteoporosis and associated symptoms. He has a medical history of NS, osteoporosis, vitamin D deficiency, hypocalciuria, hypogonadism, migraines, cervical arthritis, mild intermittent asthma controlled with an Albuterol inhaler, and a spontaneous lumbar fracture in his late 50s. He denies smoking, alcohol use, and substance use. His family history reveals significant osteoporosis affecting his mother, sister, and daughter, along with a history of stroke in his father. He reports no systemic symptoms, including fever, chills, headaches, blurry vision, oral ulcers, abdominal pain, nausea, vomiting, diarrhea, chest pain, or shortness of breath.

Table 1: Progressive Bone Mineral Density Decline in a Noonan Syndrome Patient: A 6-Year DEXA Scan Overview.

Year Since First DEXA	Lumbar Spine BMD (g/cm^2)	Lumbar Spine T-score	Hip BMD (g/cm^2)	Hip T-score
Initial	0.96	-2.4	0.78	-2.4
2 Years	0.84	-3.3	0.73	-2.8
4 Years	0.80	-3.5	0.66	-3.3
6 Years	0.798	-3.5	0.707	-2.9

DEXA, Dual-energy X-ray Absorptiometry; BMD, Bone Mineral Density; g/cm², grams per square centimeter; T-score, A measure used in medicine to describe bone density

He takes calcium carbonate 1200 mg daily, vitamin D3 1000 IU daily, Fioricet (Butalbital/Acetaminophen/Caffeine) as needed, sumatriptan 6 mg subcutaneous as needed, oxycodone-acetaminophen 10 mg-325 mg every six hours as needed, and an Albuterol inhaler as needed.

During the physical examination, the patient appeared comfortable with stable vital data and showed no signs of distress. Examination findings included normal conjunctiva, intact extraocular movements, normal ear structure and hearing, clear lungs bilaterally, regular heart sounds, normal gait and range of motion, and an oriented mental status with average mood and affect. His body mass index (BMI) was 20.99 kg/m².

Laboratory evaluations previously showed a vitamin D level of 25 ng/mL (reference range 30–100 ng/mL) and negative results for Antinuclear Antibody (ANA), celiac testing, Serum Protein Electrophoresis (SPEP), Urine Protein Electrophoresis (UPEP), and parathyroid hormone (PTH) levels within the normal range. Imaging studies revealed progressive bone density loss. Ten years before presentation to the clinic, a Dual-energy X-ray absorptiometry (DEXA) scan showed lumbar spine bone mineral density (BMD) of 0.96 g/cm² (T-score -2.4) and hip BMD of 0.78 g/cm² (T-score -2.4). Two years later, lumbar spine BMD declined to 0.84 g/cm² (T-score -3.3) and hip BMD to 0.73 g/cm² (T-score -2.8). After 4 and 6 years after the initial DEXA scan, further decreases, with lumbar spine BMD at 0.80 g/cm² (T-score -3.5) and 0.798 g/cm² (T-score -3.5) and hip BMD at 0.66 g/cm² (T-score -3.3) and 0.707 g/cm² (T-score -2.9), respectively. FRACTURES score of 17.3% 10-year probability of major osteoporotic fracture, 7.7% 10-year probability of hip fracture **(Table 1)**.

The patient sustained multiple fractures, including an L1 fracture **(Figure 1)** and a left wrist fracture in the early 60s, which were treated with kyphoplasty and wrist fixation. A year later, he underwent cervical spine surgery for chronic neck pain and used a bone growth stimulator. After another year, his DEXA scan showed L1-L4 with a T-score of -3.0 and a Z-score of -1.8. This represents a 7% improvement compared to the prior study. Bilateral hip with a mean T score of -3.0 and a Z score of -1.7. This is a 1.3% decline from the prior study. Additionally, he received an intra-articular corticosteroid knee injection for a suspected meniscus tear, which provided minimal relief of knee pain. He manages vitamin D deficiency with supplements and previously managed hypogonadism with testosterone cypionate injection, which was discontinued due to elevated PSA levels. He has declined to resume testosterone therapy.

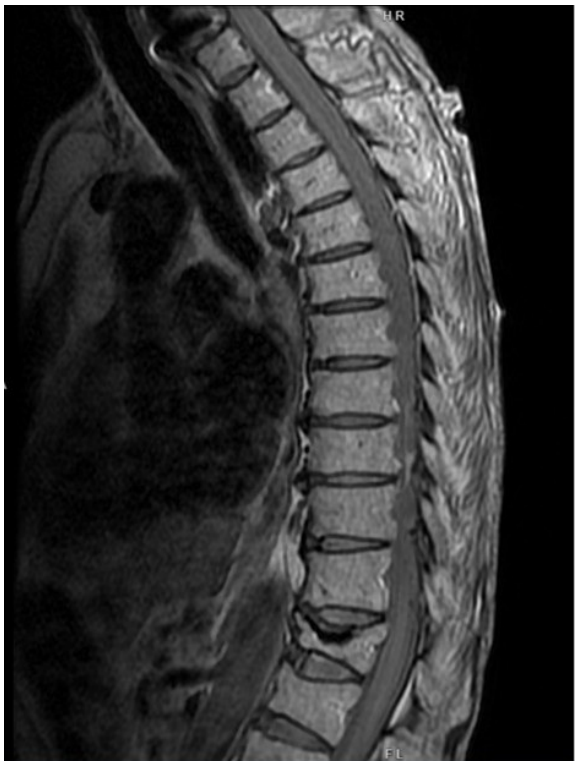

Figure 1: This MRI image shows post-kyphoplasty changes at T12 with no evidence of acute complications and a stable, mild chronic compression fracture of the L1 superior endplate.

His treatment for osteoporosis began in his mid-40s with a five-year course of Alendronate 70 mg oral weekly. After that, in the setting of worsening BMD and fracture, he completed a two-year course of teriparatide 20 mcg subcutaneously daily. At age 53, he received a single dose of zoledronic acid IV, followed by another two-year course of teriparatide 20 mcg SUBQ daily. He has been on Denosumab injection every six months for the last six years. He adhered to his medication regimen and reported no side effects.

3. Discussion

"RASopathies" refers to a group of phenotypically similar congenital disorders caused by gene mutations within the RAS/MAPK signaling pathway, a critical molecular cascade for cell division and differentiation [6]. NS is the most prevalent RASopathy, while cardiofaciocutaneous syndrome (CFC) and Costello syndrome (CS) are extremely rare, with only a few hundred cases documented worldwide [6]. Mutations in the PTPN11 gene account for about half of the genetic causes of NS [7]. Baldassare et al. found that approximately 15% of the 35% of patients with NS had compromised bone quality, as assessed by phalangeal quantitative ultrasound (QUS) [8]. Furthermore, a recent retrospective analysis of 35 individuals with NS revealed reduced axial and appendicular bone mass compared to the general population [4]. However, data on adult patients with NS remains limited.

Studies have consistently shown that BMD, used as a marker of bone health in NS, is reduced. DEXA scans, commonly employed in such evaluations, have confirmed significantly lower BMD in NS patients compared to matched controls, even when bone mineralization markers appear normal [5]. In this case, DEXA scans revealed a progression from osteopenia in 2013 to osteoporosis in

subsequent years. The patient has reduced BMD correlated with low physical activity, low muscle mass, diminished quality of life, low IGF-1 levels, pain, and bone fragility. Although Siano et al.'s case series reported elevated parathyroid hormone (PTH) levels and reduced calcitonin and vitamin D in NS patients, this case demonstrated normal PTH and vitamin D levels[9]. While PTH and vitamin D are crucial for bone metabolism and mineralization, they are not specific markers for diagnosing osteoporosis. This case aligns with previous osteoporosis reports in three adult NS patients [10, 11].

RAS/ERK hyperactivation in RASopathies, including NS, disrupts the balance between osteoclast and osteoblast activity, contributing to bone metabolic disorders [5]. Evidence suggests that mesenchymal progenitor cell differentiation, regulated by the Ras/MAPK pathway, plays a key role in osteoblast proliferation during skeletal muscle development [12]. The Ras family of GTPases (H-ras, K-ras, and N-ras) regulates this pathway by transmitting signals from the cell surface to the interior. Mutations in any component of this pathway increase MAPK activity, disrupting normal cell proliferation regulation. Hyperactivation of the RAS/MAPK/ERK pathway enhances osteoclast activity, resulting in greater bone resorption and loss. Studies in mouse models suggest that early postnatal inactivation of ERK in osteoprogenitors contributes to bone loss [13].

The PTPN11 gene encodes SHP2, a protein tyrosine phosphatase involved in regulating the proliferation, differentiation, and mobilization of mesenchymal stem cells (MSCs) and neural crest cells (NCCs) via the MAPK pathway [14]. SHP2 also plays a developmental role in chondrogenesis, mineral homeostasis, and chondrocyte transdifferentiation. Tajan et al. demonstrated that SHP2 deficiency significantly reduces the number of osteoblasts necessary for bone maturation [15]. Another pathogenic variant, the KRAS gene, has also been implicated in NS. Yang et al. recently described KRAS's role in osteogenesis, showing that small GTPase coordination in stem cells modulates autophagy, contributing to extracellular matrix accumulation [16].

Bone homeostasis involves more than the Ras/MAPK/ERK pathway. It synergizes with other signaling cascades, such as Wnt-frizzled/-catenin, BMP/SMAD/Runx2, and PI3K/AKT, which are essential for maintaining bone health. The BMP-signaling pathway enhances osteoblast differentiation through SMAD1/5/8, Runx2, and osterix activation [17]. However, SMAD3 hyperactivation interferes with osteogenic differentiation, reducing alkaline phosphatase (ALP) activity and impairing mineralization. These effects are compounded by MAPK/ERK pathway overactivity [18]. The interactions between the Ras/MAPK pathway and other cascades, like Wnt/-catenin and PI3K/AKT, remain unclear but are likely critical for bone remodeling [19].

Additional factors contributing to increased bone resorption markers in RASopathies include reduced physical activity, low serum vitamin D, and limited sun exposure, as observed in patients with neurofibromatosis type 1 (NF1) [20]. The RAS/MAPK pathway, reduced activity, and inflammatory cytokines collectively disrupt bone metabolism in RASopathy patients. Differential diagnoses include Osteomalacia, Osteogenesis Imperfecta (Mild Form), hypogonadism, Glucocorticoid-Induced Osteoporosis, and Neurofibromatosis type 1. This case is unique due to the early onset of OP in a patient with NS and the progressive worsening of BMD despite treatment with calcium and vitamin D supplementation. It underscores the importance of early detection and proactive management of osteoporosis in individuals with NS.

4. Conclusions

This case illustrates the link between Noonan syndrome and osteoporosis, highlighting the role of dysregulated RAS/MAPK signaling in bone metabolism. The progressive decline in BMD and recurrent fractures emphasize the importance of early screening and proactive osteoporosis management in NS patients. Future research should focus on developing precise genetic screening protocols to identify Noonan syndrome patients at risk for osteoporosis early in life. Additionally, investigating targeted therapeutic strategies that modulate the RAS/MAPK pathway could offer new avenues for managing and potentially reversing bone density loss in this patient population.

Conflicts of Interest

The authors declare no conflicts of interest.

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Informed consent

Obtained from the patient.

Large Language Model

None

Authors Contribution

All authors made substantial contributions to this case report. They were involved in the patient's care, the conception of the report, and the gathering of relevant clinical data. Each author participated in drafting the manuscript and revising it critically for important intellectual content. They also reviewed and approved the final version of the manuscript, ensuring its accuracy and integrity in representing the case studied.

Data Availability

The data underlying this case report are not publicly available due to privacy or ethical restrictions. The clinical data that support the findings of this case are contained within the patient's confidential medical record. Specific data excerpts that do not compromise the patient's anonymity can be made available from the corresponding author upon reasonable and ethical request.

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ASIDE Case Reports

Case Report

Volvulus of Left Descending Colon: A Case Report and Systematic Review

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ABSTRACT

Colonic volvulus has been described as the third most common cause of intestinal obstruction worldwide, with sigmoid volvulus representing more than 70% of all colonic volvulus. The descending colon is an atypical location for volvulus, with only a few documented cases in the literature. We report a case of non-viable left descending colon volvulus managed with left hemicolectomy in a 64-year-old male with no previous history of colorectal surgery. In addition, we conducted a systemic review of the literature for case reports of descending colon volvulus. We searched PubMed, Scopus, and Web of Science until November 2024 using the following search terms: (Volvulus AND "descending colon"). We extracted and summarized relevant data to better understand our case and how it compares to previously documented reports. Our search yielded seven case reports that met our inclusion criteria. Our population consisted of four males and three females, with a mean age of 49.5 years and a range of (15 to 86) years. Most of our population was over the age of 30 (5/7). The most reported symptoms were abdominal distension, colicky or cramping abdominal pain, and vomiting. Left-sided colon volvulus is a rare cause of large bowel obstruction with variable and often atypical presentations, posing diagnostic challenges. Future research should investigate anatomical and clinical predictors of volvulus, optimize imaging modalities for early diagnosis, and evaluate long-term outcomes of various surgical approaches.

1. Introduction

Volvulus describes the twisting of the intestines around its mesenteric axis, causing bowel obstruction and ischemia [1]. If not managed promptly, it can progress to bowel necrosis, necessitating resection [1]. Thus, it is considered a surgical emergency, requiring immediate recognition and intervention [1]. Although it can be presented anywhere along the intestines, the age and geographic variations have been well-described [1]. Colonic volvulus has been described as the third most common cause of intestinal obstruction worldwide [2]. Although the incidence of volvulus is relatively low in Western countries, other parts of the world feature a much higher incidence, with volvulus representing 42% of all intestinal obstructions in some parts of the world [2]. The "volvulus belt" refers to parts of Africa, South America, Russia, Eastern Europe, the Middle East, India, and Brazil, where volvulus is described to be endemic, featuring a significantly higher incidence than that seen in the West [2]. Colonic volvulus typically presents with abdominal pain, distention, constipation, and vomiting [2]. Given the non-specific symptomatology, imaging plays a key role in identifying the site of obstruction [2]. The location of the obstruction, coupled with the patient's general condition and clinical presentation, guide the management of colonic volvulus [2]. The etiology of volvulus is multifactorial, with chronic constipation, previous abdominal surgeries, and anatomical variations as predisposing factors [2]. The most common site for colonic volvulus is the sigmoid, representing more than 70% of all colonic volvulus [1]. Predisposing factors specifically associated with sigmoid volvulus include older age, diabetes, neuropsychiatric history, and institutionalization [1, 2]. Cecal volvulus, the second most common site of colonic volvulus, has been linked to young age, pregnancy, previous colonoscopy, or inadequate fixation of the colon to the peritoneum [1, 2]. Less common locations include the transverse colon, splenic flexure, and ileosigmoid [1, 2]. Given the extreme rarity of these types, there is often a delay in diagnosis and treatment, with many cases progressing to bowel necrosis and an alarming mortality rate [2]. Descending colon volvulus is another atypical location for volvulus, with only a few documented cases in the literature [3]. The infrequent occurrence is likely attributed to its retroperitoneal position and the absence of a mesentery [3]. We report a unique case of volvulus of the descending colon encountered at Alexandria Main University Hospital. In addition, we aim to systematically review the literature for all previously documented cases of volvulus of the descending colon. In doing so, we can identify patterns and explore proposed mechanisms to understand this rare occurrence better. Enhanced understanding can lead to earlier recognition and prompt management, ultimately improving outcomes.

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Table 1: Lab investigations of the patient on admission

Labs	Result	References
HGB	12.5	13.0 – 17.0 g/dL
HCT	33.60	39.0 – 50.0%
MCV	93.1	80.0 – 100.0 fL
MCH	34.6	27.0 – 34.0 pg
MCHC	37.2	32.0 – 36.0 g/dL
RBC	3.61 $\times 10^6$	4.2 – 5.9 $\times 10^6$/mm³
PLT	259 $\times 10^3$	150 – 400 $\times 10^3$/mm³
WBCs	12.2 $\times 10^3$	4.0 – 11.0 $\times 10^3$/mm³
BASO	0.10	0 – 1%
EOS	2	1 – 4%
NEUT	65.90	50 – 70%
LYMP	29	20 – 40%
MONO	3	2 – 8%
ALT	25.1	7 – 56 U/L
BILI T	1.7	0.1 – 1.2 mg/dL
CREAT	0.95	0.7 – 1.3 mg/dL
RBG	82.1	70 – 140 mg/dL
PT	12	11 – 13.5 sec
INR	1	0.8 – 1.1

HGB, Hemoglobin; HCT, Hematocrit; MCV, Mean Corpuscular Volume; MCH, Mean Corpuscular Hemoglobin; MCHC, Mean Corpuscular Hemoglobin Concentration; RBC, Red Blood Cells; PLT, Platelets count; WBC: White Blood Cell; BASO: Basophil; EOS: Eosinophil; NEUT: Neutrophil; LYMP: Lymphocyte; MONO: Monocyte; ALT: Serum Alanine Transaminase; BILI T: Bilirubin, Total; CREAT: Serum creatinine; RBG: Random Blood Glucose; PT: Prothrombin Time; INR: International Normalized Ratio.

2. Case Presentation

A 64-year-old male presented to the emergency department at Alexandria Main University Hospital complaining of severe paraumbilical pain, abdominal distention, and four days of absolute constipation. The patient denied vomiting, bloody stool, loss of appetite, chronic constipation, and weight loss. He noted intermittent abdominal cramping, bloating, and mild dizziness for a few weeks prior.

The patient is a farmer. His medical history is positive for two epigastric fatty hernias diagnosed 30 years ago without surgical repair. His medical history is negative for hypertension, diabetes, neurological conditions, and psychiatric illnesses. His only surgical history was nephrolithotomy 19 years ago with no complications. The patient is not taking any medications and has no relevant family history.

On admission, his vital signs were stable (blood pressure = 140/90 mmHg, heart rate = 80 beats/minute, temperature = 36.6°C). Physical examination revealed a well-healed surgical scar in the flank region. The abdomen was distended and mildly tender, with no hyperactive bowel sounds. A digital rectal examination revealed an empty rectum with no stool. CBC showed mild normocytic normochromic anemia (hemoglobin 12.5 g/dl), mild leukocytosis (12.2× 103/mm3), and elevated total bilirubin (1.7 mg/dl). Lab investigations were otherwise unremarkable **(Table 1)**. An erect plain abdominal X-ray showed omega signs and air-fluid levels, suggesting a volvulus **(Figure 1)**. CT revealed a distended descending colon measuring 15.6 cm in diameter.

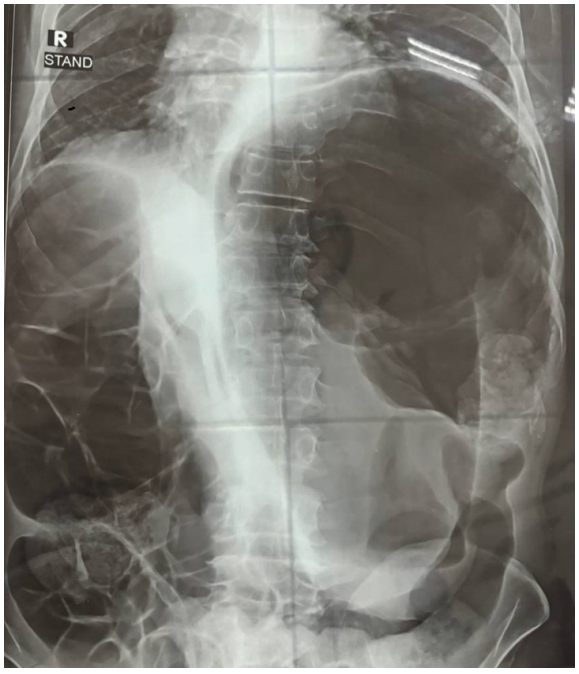

Figure 1: Abdominal plain X-ray showing an omega sign

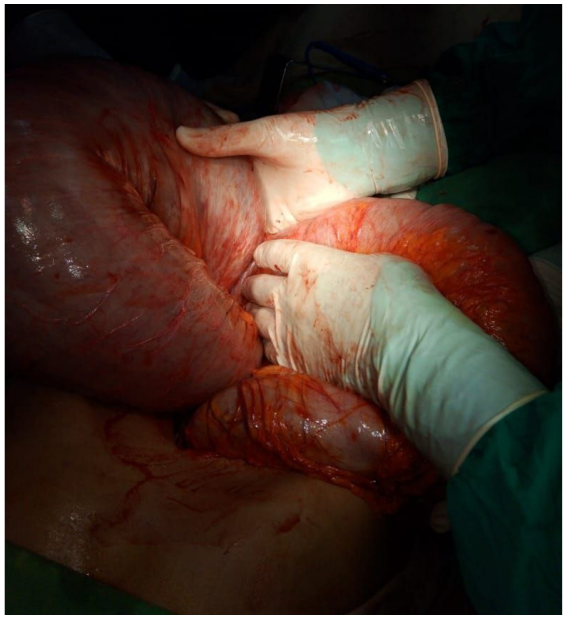

Figure 2: Intraoperative findings showing an unviable 360° clockwise rotated descending colon with a thin wall

Intraoperative findings revealed an unviable 360° clockwise rotated descending colon with a thin wall and persistent mesocolon **(Figure 2)**. A left hemicolectomy with a double-barrel stoma was performed. There were no postoperative complications, and the patient was discharged on the sixth day postoperatively. He followed up at the outpatient clinics one week after discharge and then every two weeks until the stoma reversal four months later.

3. Methods

3.1. Literature search strategy

In this systematic review, we searched the following databases: PubMed, Scopus, and Web of Science from inception until November 2024. We used the following search terms: ((Volvulus OR "Torsion of the bowel" OR "Intestinal torsion" OR "Bowel torsion" OR "Twisted bowel") AND ("Descending colon" OR "Colon descendent" OR "Left-sided colon" OR "Distal colon" OR "Left colonic segment" OR "Descending large intestine")).

3.2. Eligibility criteria

We included case reports of left descending colon volvulus. Studies reporting volvulus in other colonic segments were excluded. Additionally, we excluded conference abstracts, reviews, and inaccessible full texts. We had no restrictions on non-English articles.

3.3. Study selection and data extraction process

After exporting the retrieved articles, we removed duplicates. Two authors independently screened the articles in a two-stage process to determine their eligibility for inclusion in our systematic review. This included an initial title and abstract screening and subsequent full-text screening, utilizing Rayan software [4]. Discrepancies were resolved through discussion. Two independent authors used an Excel sheet to extract data from the included case reports. The extracted variables included Study ID, patient demographics (gender/age, geographic location), relevant comorbidities, surgical history, presenting symptoms, symptom duration before diagnosis, degree of torsion, and management details. We also extracted data from our case report.

3.4. Methods for the case report

We report a rare left descending colon volvulus case at Alexandria Main University Hospital. We included demographic information, relevant medical history, presenting symptoms, X-ray imaging findings, laboratory results, and an intraoperative picture. We also included notable clinical findings and interventions. This case report is reported in accordance with the CARE checklist guidelines.

4. Results

Our primary literature search identified 301 records. After removing duplicates, 204 publications were retained. After screening titles and abstracts, 31 manuscripts remained. Following the full-text screening, 24 articles were excluded, leaving seven studies that met our inclusion criteria [3, 5, 6, 7, 8, 9, 10]. **(Figure 3)** is a flowchart illustrating the screening and selection process, including our case report.

Most of the population included in our review (N = 7) were above the age of 30 (5/7). The mean age was 49.5 years, ranging from 15 to 86 years. Four of the patients were males, and three were females. The most reported symptoms among the seven patients presenting with descending colon volvulus included abdominal distension, colicky or cramping abdominal pain, and vomiting [3, 5, 7, 10]. Two patients experienced an inability to pass feces or flatus [3, 5], while one had progressive abdominal distension with pain rated 6–7 on the pain scale [7]. Vomiting, when present, was often bilious, foul-smelling, and non-projectile. The pain varied in location, with some patients reporting left-sided pain and others reporting right hypochondriac pain. One patient reported dyspnea accompanying the left lower quadrant pain.

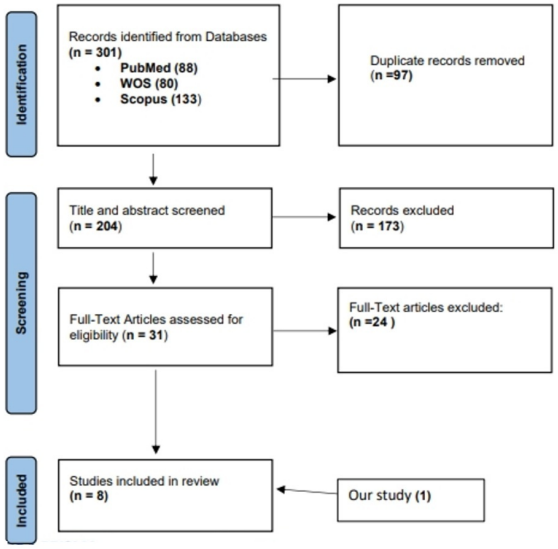

Figure 3: PRISMA flow diagram of study selection.

Management of the cases included a variety of approaches based on severity and underlying pathology. Initial resuscitation, including IV fluids and antibiotics, was common, with some requiring exploratory laparotomy due to unsuccessful rectal tube deflation. Definitive interventions included detorsion with rectal tubes or transanal ileus tubes, endoscopic decompression, and segmental resections with colostomy or primary anastomosis. Additional interventions included laparoscopic fixation of the colon to the abdominal wall in some cases. Postoperative outcomes were largely uneventful. Discharge timelines ranged from 5 to 7 days postoperatively. Follow-up of three patients at 6 months showed stable outcomes, with no reported recurrence of symptoms [3, 8, 9]. The summary of included studies and patient characteristics is in **(Table 2)**.

5. Discussion

Colonic volvulus is the third most common cause of colonic obstruction, after colon cancer and diverticulitis. This condition arises from the rotation of the intestine around its mesenteric axis, leading to partial or complete obstruction, which may progress to ischemia or perforation [11].

Volvulus typically occurs in sections of the colon with a mesentery, such as the sigmoid, cecum, and transverse colon [6]. The descending colon is a retroperitoneal structure typically surrounded by peritoneum on three sides and lacking a mesocolon. However, between the fourth and fifth months of gestation, the primitive dorsal mesocolon may fail to fuse with the parietal peritoneum, resulting in a persistent descending mesocolon [12]. This decreases the stability of the descending colon, resulting in considerable positional variation. The descending colon may shift toward the midline, creating a space for the small bowel to migrate. Although chronic constipation may cause a redundant and dilated colon associated with an elongated mesocolon, its absence in our patient suggests that other factors, such as congenital anatomical variations or idiopathic mechanisms, may have contributed to the development of volvulus [13].

Table 2: Shows a summary of the included studies

Study ID	Gender/Age	Geographic location	Relevant comor-bidities	Surgical history	Symptoms	Duration of symptoms before diagnosis	Degree of torsion	Management
Marey 2025 (This case)	M/64	Egypt	None	Nephrolithotomy	severe paraumbilical pain, abdominal distention, and four days of absolute constipation.	4 days	360 deg clockwise	A left hemicolectomy with a double-barrel stoma was performed
Abebe 2024 [3]	M/75	Ethiopia	BPH	Laparotomy plus sigmoidectomy with end-to-end descending Colorectal anastomosis for sigmoid volvulus.	Failure to pass feces & flatus, colicky abdominal pain, abdominal distension, and two episodes of vomiting, which were bilious, non-projectile, foul smelling, and non-bloody.	1 day	360 deg counterclockwise	IV Ringer's lactate. Unsuccessful deflation with rectal tube. Exploratory laparotomy. Deflated with rectal tube intra-op.
Ata 2019 [6]	M/28	Lahore	NA	NA	A single episode of vomiting, constipation, colicky abdominal discomfort, more in the left hemi-abdomen.	NA	180 deg	Midline laparotomy, resection of redundant colonic segment, double barrel colostomy stomas.
Chen 2003 [10]	F/51	Taiwan	CC	None	Cramping abdominal pain	6 days	720 deg clockwise	Derotation & segmental colectomy with primary end-to-end anastomosis.
Huynh 2020 [8]	M/86	Australia	PD	Curative laparoscopic low anterior resection for a rectal adenocarcinoma.	NA	NA	NA	Successful endoscopic decompression. Laparoscopy & colopexy. Adhesions fusing transverse colon mesentery to the neo-L colon were divided. Interrupted polypropylene sutures were used to fix the neo-L colon to the post-gastric and Lower lateral abdominal walls.
Ito 2022 [9]	F/15	Japan	NA	NA	Right hypochondriac pain	NA	organo-axial, clockwise 270 deg	Endoscopic detorsion of the colon was performed, a transanal ileus tube was inserted, and elective laparoscopic fixation of the descending colon was performed. The left colon was sutured to the Left abdominal wall to form the splenic flexure & SDJ.
Kebede 2024 [7]	M/55	Ethiopia	None	Hartman procedure for sigmoid volvulus and end colostomy, then colostomy reversion, descending colon-rectum end-to-end anastomosis.	Progressive abdominal distension with colicky persistent abdominal pain and 2 episodes of vomiting with the ability to pass feces & flatus.	1 day	360 deg counterclockwise	Resuscitation with saline, IV antibiotics, NGT, rectal tube deflation (failed). Exploratory laparotomy, then Hartmann's resection of the descending colon. A second surgery (Hartmann's colostomy was reversed & transverse colorectal anastomosis was performed) after 3 months.
Marshak 2014 [5]	F/36	US	SLE	NA	Worsening dyspnea & LLQ pain (4 days). Abdominal distension with inability to pass flatus (2 days).	2 days	NA	Emergent colonoscopy leading to successful detorsion. A repeated colonoscopy 2 days later demonstrated descending and transverse colons were redundant and tortuous.

M, Male; F, Female; BPH, Benign Prostatic Hyperplasia, CC, Chronic Constipation; PD, Parkinson's Disease; SLE. Systemic Lupus Erythematosus; LLQ, Left Lower Quadrant; IV, Intravenous; NGT, Nasogastric tube; SDJ, Sigmoid-Descending Junction

The persistent mesocolon observed intra-operatively and the patient's intermittent cramping and bloating over several weeks suggest that this may have been the etiology underlying volvulus in our patient. The anatomical arrangement of a long redundant descending colon with a persistent mesocolon facilitates torsion.

Based on our systematic review of the previously documented cases, there may be a pattern of association between the history of previous abdominal surgery and the incidence of descending colon volvulus. For instance, one case had a prior sigmoidectomy with end-to-end anastomosis for sigmoid volvulus [3]. Other cases featured a previous laparoscopic low anterior resection for rectal adenocarcinoma or a Hartmann procedure for gangrenous sigmoid volvulus. Notably, in one patient, the reversal of a Hartmann colostomy required mobilizing the distal descending colon and rectum to achieve tension-free anastomosis, but he experienced recurrent constipation thereafter [7]. These histories highlight the descending colon's vulnerability to recurrent pathology and emphasize the need to take this into account in surgical planning and follow-up. In contrast to the examples mentioned previously, our patient did not have a history of colorectal surgery or other significant abdominal operations except for nephrolithotomy, further highlighting the uniqueness of this case.

This case report and systematic review aim to deepen the understanding of volvulus presentations and management, particularly in the left descending colon. Notably, our case presented differently from those previously reported in the literature. Our patient had normal vital signs and lacked the hyperactive bowel sounds commonly observed in previously documented cases of volvulus in the left descending colon [3, 7]. Additionally, the patient did not report vomiting, in contrast to prior cases, emphasizing the presentation variability. Accurate diagnosis of left descending colon volvulus might be difficult since it can resemble other causes of large bowel obstruction, such as sigmoid volvulus, colonic neoplasms, toxic megacolon, and severe diverticular disease. To distinguish between these disorders, it is necessary to carefully evaluate the clinical presentation, imaging results, and, in certain situations, surgical exploration to confirm the presence of a volvulus.

Our patient's erect plain abdominal X-ray showed an omega sign and air-fluid levels, suggesting volvulus. However, the exact site of obstruction was hard to determine due to the limitations of X-ray imaging. Although barium enema is sometimes used alongside standard radiography for diagnosing colonic volvulus, we opted for CT as barium enemas have limited utility in detecting complications of volvulus. CT imaging is the gold standard for colon volvulus diagnosis because it can distinguish it from other types of bowel obstruction and show the distinctive "whirl sign" of twisted mesentery, which was originally described for midgut volvulus. It can also aid in identifying sigmoid and cecal volvulus [14, 15, 16]. The whirl sign represents a tightly twisted bowel, mesentery, and vessels, with the tightness reflecting the rotation's severity. CT can also reveal signs of strangulation, such as bowel wall thickening and hemorrhagic mesenteric fluid [15].

The surgical management of colonic volvulus varies based on its clinical presentation and the location of the obstruction. Initial management often includes colonoscopic detorsion and decompression in cases without signs of necrosis or perforation. This approach allows for a semi-elective resection and anastomosis once the patient stabilizes, improving the chances of a definitive, single-stage procedure. Detorsion without resection has a high recurrence rate. If endoscopic methods fail, surgical intervention becomes necessary [17, 18].

In cases where necrosis or perforation is evident, such as with a 360° clockwise rotated descending colon, surgery is essential. This involves resecting the affected segments, choosing between ostomy (e.g., double-barrel stoma) or primary anastomosis, depending on the condition of the bowel and the patient's stability [19]. Our patient had an uneventful postoperative recovery and remained asymptomatic without complications following surgery at a four-month follow-up till the stoma reversal. Based on our systematic review, recurrence of left descending colon volvulus is rare. Still, cases with underlying anatomical abnormalities or prior volvulus episodes may have a risk of recurrence, emphasizing the need for long-term monitoring.

Despite the insights provided by this systematic review and case report, several limitations must be acknowledged. The rarity of descending colonic volvulus and its variable presentation challenge the generalizability of findings. The limited availability of standardized data on persistent descending mesocolon anatomy and its clinical implications further constrains our understanding. Additionally, most cases are documented as isolated reports, lacking robust, large-scale evidence to inform best practices. Future research should investigate anatomical and clinical predictors of descending colon volvulus, optimize imaging modalities for early diagnosis, and evaluate long-term outcomes of various surgical approaches. A comprehensive registry of colonic volvulus cases would also facilitate a better understanding and management of this uncommon but clinically significant condition.

6. Conclusions

Left-sided colon volvulus is a rare cause of large bowel obstruction with variable and often atypical presentations, posing diagnostic challenges. Our case underscores the importance of maintaining a high index of suspicion and prioritizing CT imaging for its superior ability to detect volvulus and complications like ischemia.

Conflicts of Interest

The authors declare no conflicts of interest.

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Informed consent

Obtained from the patient.

Large Language Model

None

Authors Contribution

MMM Conceptualization; methodology; validation; visualization; writing the original draft. MAH Visualization: methodology; writing the original draft. MHE Visualization: writing the original

draft. BAMS Validation: writing the original draft. TAE Supervision.

Data Availability

All data supporting the findings of this study are included in the article. Additional information is available from the corresponding author upon reasonable request.

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Case Report

Hyponatremia-Induced Rhabdomyolysis in a Patient with Psychogenic Polydipsia: A Case Report

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ABSTRACT

Hyponatremia is a common electrolyte abnormality that can lead to various complications, including rhabdomyolysis. Observational studies have identified a correlation between hyponatremia and the occurrence of rhabdomyolysis in hospitalized patients. We report a 45-year-old male with a medical history of hypertension, hyperlipidemia, and a congenital neurological defect featuring an 8 cm right frontal porencephalic cyst communicating with the right lateral ventricle, colpocephaly, congenital left hemiparesis, paranoid schizophrenia, anxiety, and depression. He presented with rhabdomyolysis caused by hyponatremia and aggravated by psychogenic polydipsia. A hyponatremic state caused by psychogenic polydipsia may induce rhabdomyolysis in patients with a genetic predisposition. Hence, monitoring muscle markers in these patients is crucial, with further evidence needed to establish hyponatremia as the primary cause of rhabdomyolysis in the absence of other confounders.

1. Introduction

Hyponatremia frequently occurs as an electrolyte disorder and causes several complications, including rhabdomyolysis [1] Rhabdomyolysis is a clinical and biochemical condition that occurs when injured muscle tissue releases its proteins and electrolytes into the bloodstream, causing heart and kidney injury and permanent disability or even mortality [2]. Observational studies [3, 4, 5] have established hyponatremia as a risk factor for rhabdomyolysis in hospitalized patients, particularly in settings of rapid sodium correction, extreme physical exertion, or comorbid metabolic disturbances. However, existing literature mostly focuses on hospitalized patients with apparent risk factors, leaving gaps in understanding the condition's presentation and management in non-hospitalized individuals. Although hyponatremia-induced rhabdomyolysis is uncommon, it represents a serious complication with significant renal morbidity. Our study presents a case report of hyponatremia-induced rhabdomyolysis with atypical presentation in a non-hospitalized patient with mild hyponatremia and no traditional triggers.

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2. Case presentation

A 45-year-old male with a history of hypertension, hyperlipidemia, and an 8 cm right frontal porencephalic cyst communicating with the right lateral ventricle, colpocephaly, congenital left hemiparesis, paranoid schizophrenia, anxiety, depression, and psychogenic polydipsia experienced an episode of loss of consciousness. Witnesses reported that the patient often visited his favorite fast-food restaurants and requested large water refills to prolong his stay. Emergency medical services found him unresponsive on the floor of a fast-food restaurant for approximately two minutes.

At the Emergency Department (ED), his blood pressure measured 141/73 mmHg, his heart rate was 82 beats per minute, his temperature was 97.5°F, his respiratory rate was 18 breaths per minute, and his oxygen saturation was 95% on room air. Upon examination, the patient appeared lethargic but was awake, cooperative, and oriented to person, place, and time. He was normocephalic and atraumatic on physical exam. Trace bilateral lower extremity pitting edema was observed, but no signs of volume overload were present. Although he could follow commands, his level of alertness prevented a full neurological assessment.

Laboratory findings revealed hyponatremia (111 mmol/L), hypochloremia (77 mmol/L), hypomagnesemia (1.5 mg/dL), hypocalcemia (8.2 mg/dL), and normal serum glucose. Additional findings included mild leukocytosis ($11.57 \times 10^3/\mu L$) and an elevated venous lactate level (3.2 mmol/L). Serum creatine kinase (CK) levels were markedly elevated at 3571 U/L **(Tables 1 and 2)**.

Table 1: Blood work done at the ED and ICU

Lab (Reference Range)	Reference Range	Result
Hemoglobin	14–18 g/dL	11.9 g/dL
Hematocrit	42–52%	33.4%
White blood cells	4.8–10.8 × 10^3/mcL	11.57 × 10^3/mcL
Platelets	150–450 × 10^3/mcL	219 × 10^3/mcL
Blood glucose	74–110 mg/dL	109 mg/dL
Sodium	136–145 mmol/L	111 mmol/L
Potassium	3.5–5.1 mmol/L	3.4 mmol/L
Chloride	98–108 mmol/L	77 mmol/L
Magnesium	1.6–2.6 mg/dL	1.5 mg/dL
Calcium	8.6–10.3 mg/dL	8.2 mg/dL
Phosphorus	2.5–4.5 mg/dL	3.7 mg/dL
BUN	6–23 mg/dL	8 mg/dL
Creatinine	0.7–1.2 mg/dL	0.64 mg/dL
Venous pH	7.32–7.43	7.45
Venous PO_2	30–50 mmHg	65 mmHg
Venous PCO_2	41–54 mmHg	31 mmHg
Venous HCO_3	22–29 mmol/L	22 mmol/L
Venous lactate	0.6–1.4 mmol/L	3.2 mmol/L
Albumin	3.5–5.2 g/dL	4.4 g/dL
Total bilirubin	0–1.2 mg/dL	1.3 mg/dL
Direct bilirubin	0–0.3 mg/dL	0.2 mg/dL
Alkaline phosphatase	40–129 U/L	59 U/L
ALT	0–41 U/L	38 U/L
Serum ammonia	16–60 µmol/L	51 µmol/L
Creatinine kinase	20–190 U/L	3571 U/L
Valproic acid level	50–100 µg/mL	41.8 µg/mL
Prolactin	4.1–18.4 ng/mL	13 ng/mL
Serum AM cortisol	6–18.4 µg/dL	6.6 µg/dL
TSH	0.27–4.2 µIU/mL	1.15 µIU/mL
Serum osmolality	285–303 mOsm/kg	264 mOsm/kg

Table 2: Urine work-up

Lab (Reference Range)	Reference Range	Result
Specific gravity	1005–1030	≤1005
Osmolality	50–1200 mOsm/kg	106 mOsm/kg
Random urea	—	31 mg/dL
Random chloride	—	11 mmol/L
Random sodium	—	44 mmol/L
Random potassium	—	4 mmol/L

The ED administered 2 liters of intravenous normal saline. A CT scan of the head showed no acute intracranial abnormalities, and chest imaging was unremarkable.

The patient was admitted to the intensive care unit (ICU) for close monitoring and gradual correction of sodium levels. Clinicians discontinued intravenous fluids, implemented fluid restriction, and corrected other electrolyte disturbances. A two-hour electroencephalogram (EEG) showed no seizure activity, and serum prolactin levels at admission (13 ng/mL; reference: 4.1–18.4 ng/mL) indicated no evidence of seizures. Over 36 hours, sodium levels were corrected to 143 mmol/L, and CK levels decreased to 124 U/L. The patient's symptoms improved, and he remained seizure-free during his hospitalization. After stabilization, he was discharged with instructions for outpatient follow-up.

3. Discussion

Psychogenic polydipsia manifests as a clinical disorder characterized by polyuria and polydipsia, which commonly affects psychiatric populations, particularly individuals with schizophrenia [6]. Although the exact mechanism by which psychogenic polydipsia leads to hyponatremia remains unclear, researchers attribute it to an increase in total body water relative to total body sodium content, which dilutes blood sodium levels [7].

Health practitioners frequently encounter hyponatremia in clinical practice but often fail to recognize its association with rhabdomyolysis. Malfunctioning of the sodium/calcium pump appears to drive the development of rhabdomyolysis in hyponatremic states by activating proteases and lipases that cause cell lysis [8]. While evidence linking low serum sodium levels to muscle breakdown continues to grow, a study involving animal models refuted a direct causal association between hyponatremia and rhabdomyolysis. Instead, factors such as genetic predispositions and convulsive states are well-established contributors [9]. Trimarchi et al. reviewed a case in 1999 involving acute excessive water ingestion and severe muscle pain in a patient on chronic hydrochlorothiazide therapy. The case demonstrated hyponatremia-induced rhabdomyolysis, emphasizing the importance of maintaining a high level of suspicion in patients presenting with acute muscle pain and hyponatremia. They recommended serial monitoring of muscle enzymes in such cases [10].

Several reports have identified hyponatremia as a trigger for rhabdomyolysis in patients using certain medications. For instance, myopathy has been documented with indapamide, a drug linked to hypokalemia and hyponatremia [11]. Similarly, severe rhabdomyolysis and hyponatremia were reported in patients using bisacodyl and picosulphate for bowel preparation before colonoscopies [12]. Increased water intake during competitive sports often disrupts fluid and electrolyte balance, particularly sodium levels. Studies have shown that ultra-endurance athletes experience higher rates of rhabdomyolysis in hyponatremic states compared to non-hyponatremic counterparts. This was evident in an investigation of exercise-associated hyponatremia and rhabdomyolysis across seven races and disciplines [13].

4. Conclusion

Recurrent rhabdomyolysis has been observed in cases of psychogenic polydipsia-induced hyponatremia, underscoring the importance of monitoring muscle markers in patients with severe hyponatremia. Although our case does not confirm seizures as a cause of myopathy, further research is necessary to establish hyponatremia as the primary cause of rhabdomyolysis in the absence of other confounders.

Conflicts of Interest

The authors declare that they have no competing interests.

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Informed consent

Written consent for publication was obtained from the patient involved in this case report.

Large Language Model

None

Authors Contribution

HA contributed to case identification and drafting the main manuscript. TA was responsible for the case presentation. PM wrote the introduction section. OA and A contributed to the discussion. AH served as the corresponding author and performed the manuscript review.

Data Availability

All the data is available with the corresponding Author upon request

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ASIDE Case Reports

Case Report

Thyroid Hormone Resistance Syndrome: A Case Report with Literature Review

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ABSTRACT

Resistance to thyroid hormone receptor beta (THRβ) is a rare condition causing abnormal thyroid function tests (TFTs) characterized by elevated thyroid hormone levels with unsuppressed Thyroid Stimulating Hormone (TSH). Thyroid hormone action involves multiple steps, and mutations affecting these steps are key to understanding and managing thyroid disorders. We present a case of THRβ resistance associated with cardiac arrhythmia. A 40-year-old male with a history of atrial fibrillation (AF) was referred for evaluation of abnormal TFTs and thyroid nodules. TFTs revealed a normal TSH and elevated free thyroxine. Imaging showed a large, peripherally enhancing necrotic mass with calcification in the left thyroid lobe and a 0.8 cm hypodense area in the right lobe. Thyroid ultrasound confirmed bilateral nodules, with the largest in the lower pole of the left lobe. The fine-needle aspiration biopsy was benign (Bethesda category II). Inherited THRβ pathogenic variants cause thyroid hormone resistance, often resulting in an enlarged thyroid gland. Despite this resistance, patients may still show clinical signs of cardiac arrhythmias. Diagnosing thyroid hormone resistance helps avoid unnecessary treatment for asymptomatic patients.

1. Introduction

Thyroid hormone resistance (THR) is a rare genetic condition where tissues respond poorly to thyroid hormones [1]. Mutations in the thyroid hormone receptor beta (THRβ) gene cause about 85% of cases, with over 100 mutations identified. Neomutations account for the remaining 15%, meaning affected individuals may lack a family history of the disorder unless they pass it on to their children [2]. Researchers have classified THRβ into subtypes to improve understanding and treatment [3]. Clinicians describe it as "generalized" when patients are euthyroid and as "pituitary resistance" when hyperthyroid symptoms appear, as reported by Guo et al. [4, 5]. They use the term "isolated peripheral THR" when TSH decreases after high doses of liothyronine (L-T3) without hyperthyroid symptoms, documented in one patient [6]. Genetic classifications identify THR as either homozygous or heterozygous, with subtypes based on mutation characteristics [3]. Most cases involve heterozygous dominant-negative THRβ mutations, resulting in defective receptors. Only four homozygous cases have been reported, showing severe symptoms like growth restriction, vision and hearing impairments, and cardiac anomalies [7]. Although most patients with THR remain euthyroid, some show symptoms of hypothyroidism or hyperthyroidism [3]. Elevated free thyroid hormone levels with a non-suppressed TSH serve as the primary diagnostic indicator of tissue hyporesponsiveness [5]. Studying family members with similar thyroid test results can confirm the genetic basis of the disorder and reveal variability in thyroid hormone sensitivity [4]. Currently, no treatment can fully correct the defect in THR [6]. However, most individuals naturally compensate by increasing thyroid hormone production, often eliminating the need for medical intervention [7]. This article presents a case of THRβ with cardiac arrhythmia, confirmed through genetic testing.

2. Case Presentation

A 40-year-old man with a history of atrial fibrillation (AF) presented to the endocrinology clinic for evaluation of abnormal thyroid function tests (TFTs) and a thyroid nodule. He had recently been hospitalized for AF with a rapid ventricular response. He also had a history of receiving a two-month course of amiodarone treatment three years earlier. Initially, we found discrepant TFTs in which TSH was 1.375 (normal range: 0.55–4.78) and Free Thyroxine (fT4) was elevated at 2.76 (normal range: 0.89 – 1.76). Regarding imaging studies, a neck computed tomography (CT) scan showed a large, peripherally enhancing mass with central necrosis and calcification encompassing nearly the entire left thyroid lobe ($2.2 \times 3.6 \times 4.6$ cm). The scan also identified a 0.8 cm hypodense area in the right thyroid lobe. Thyroid Ultrasound: Bilateral thyroid nodules were present, with the largest nodule in the lower pole of the left lobe **(Figure 1)**. Regarding Fine Needle Aspiration (FNA) Biopsy, the left thyroid nodule showed Bethesda Category II findings, including benign-appearing follicular cells and abundant colloid. MRI brain ruled out TSH-secreting adenoma. He reported

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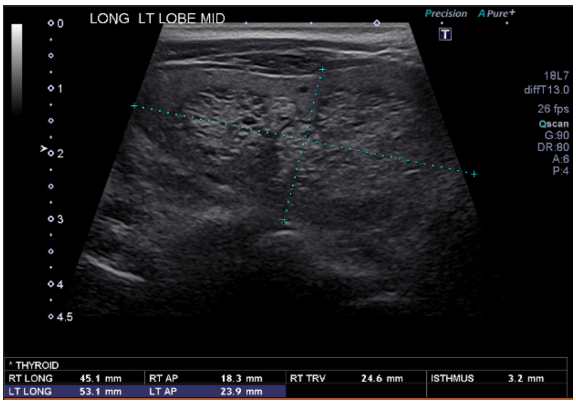

Figure 1: Thyroid ultrasound showed nodules bilaterally, with the largest one at the lower pole of the left lobe.

thyroid abnormalities in his son and brother but was unable to provide details. He was referred for genetic screening, which showed THRβ with a pathogenic variant: c.9628>G (p.Y321C)

3. Discussion

THR is a rare clinical syndrome marked by reduced sensitivity to thyroid hormone, primarily caused by mutations in the THRβ gene. THRβ affects approximately one in 40,000 individuals [8, 9]. Specific genetic mutations cause wide variations in its pathogenesis, influencing symptoms and signs. Refetoff et al. first described THRβ resistance in 1967, and Sakurai et al. identified the initial THRβ gene mutation in 1989 [3, 10, 11]. THR is characterized by elevated thyroid hormone levels with normal or slightly increased TSH levels [12]. Assay interference, such as interfering antibodies (anti-streptavidin, anti-ruthenium, heterophilic, or anti-T4/T3 antibodies), substances like biotin, treatments including heparin or nonsteroidal anti-inflammatory drugs, and changes in thyroid hormone transport proteins (albumin, transthyretin, and thyroxine-binding globulin) can cause these paradoxical biochemical findings. A TSH-secreting pituitary adenoma (TSH-oma) also serves as a significant differential diagnosis for THR [13, 3]. Campi et al. reported that 12% of 100 subjects with inappropriate TSH secretion were misdiagnosed, including a patient with THRβ resistance initially diagnosed with a TSH-producing tumor [14]. Several cases have highlighted the challenges of accurate diagnosis. Liao et al. documented a 54-year-old woman misdiagnosed with a TSH-oma, who showed no improvement after transsphenoidal surgery; genetic studies later confirmed THRβ [15, 16, 17, 18]. In Taiwan, Liu et al. described a 10-year-old boy with goiter misdiagnosed as having hyperthyroidism, but molecular studies eventually revealed THRβ [19]. Most patients showed no symptoms because excess thyroid hormone production compensated for tissue resistance [20]. When symptoms did appear, the primary clinical features of THRβ included goiter (66%-95%), emotional disturbances (60%), attention deficit hyperactivity disorder (ADHD) (40%-60%), sinus tachycardia (33%-75%), and hearing impairment [21, 22, 12]. Less common features included variable degrees of mental retardation, short stature with reduced subischial leg length, chronic constipation, and bradycardia [22]. In our case, initial TFTs showed normal TSH but elevated fT4 of 2.76. Imaging revealed a large mass in the left thyroid lobe with calcifications and additional nodules bilaterally. FNA biopsy indicated benign findings (Bethesda category II). Despite persistently elevated fT4 and normal TSH, the patient remained clinically euthyroid for 1.5 years. Repeat labs eventually showed elevated TSH and fT4, but the MRI ruled out a TSH-oma. Genetic screening identified a pathogenic variant in the THRβ gene, which explained the thyroid abnormalities. Ferrara et al. reported three THR cases with homozygous THRβ mutations causing mental retardation, tachycardia, goiter, hearing loss, and growth retardation [23]. Takeda et al. described a case with a complete absence of both THRβ alleles [24, 25], while Usala et al. documented an amino acid deletion causing THRβ [26]. Heterozygous cases showed variable symptoms based on tissue resistance and mutant TRβ protein expression [12]. THR has also been linked to congenital hypothyroidism, thyroid dysgenesis, and ectopic thyroid tissue, with five cases reported [27, 28, 29, 30, 31]. ADHD is present in 48-83% of patients, typically treated with standard methods. L-T3 has been effective in refractory cases, improving insomnia and hyperactivity[32, 33]. In 2017, Moran et al. reported a pediatric homozygous THRβ resistance case with dilated cardiomyopathy and thyrotoxicosis, treated with Triac and methimazole, leading to reduced thyroid hormone, normal TSH, and improved growth and cardiac function [34]. A large retrospective study revealed three key findings regarding THRβ resistance during pregnancy: A) higher miscarriage rates in pregnancies with THRβ resistance and unaffected fetuses; B) unaffected infants born to mothers with THRβ resistance had lower birth weights, possibly due to excess thyroid hormone crossing the placenta; and C) affected infants had normal birth weights due to impaired thyroid hormone sensitivity [22]. Treatment for pregnant women with THRβ resistance should be individualized, considering past pregnancy history and fetal genotype after amniocentesis [22]. Kahaly et al. examined the cardiovascular traits of patients with THRβ in comparison to those with hyperthyroidism, hypothyroidism, and euthyroid controls. Their study found that 26% of THRβ patients experienced tachycardia, 32% reported palpitations, 4% had dyspnea, 6% developed atrial fibrillation, and 4% exhibited mitral valve prolapse. These symptoms were less common and milder than in hyperthyroid patients. Additionally, the echocardiographic analysis revealed that the cardiac systolic and diastolic functions of THRβ patients were between those of hyperthyroid and euthyroid individuals [35]. THR treatment is individualized, as no curative therapy exists for THRβ defects [3]. Synthesized TH analogs and Roxadustat show promise in vitro but lack in vivo results [36], [37]. TSH suppression with high-dose T3 effectively reduces goiter size, avoiding surgery due to high recurrence rates [38]. Most THR-related thyroid nodules are benign, though some cases of papillary carcinoma require thyroidectomy and radioactive iodine, often resulting in poor outcomes. 3,3,5-Triiodothyroacetic Acid (Triac), combined with levothyroxine, beta-blockers, and calcium/vitamin D, has shown success in managing symptoms like tachycardia, attention deficits, and goiter [39, 40, 3].

4. Conclusions

THRβ resistance is an uncommon and often underdiagnosed endocrine disorder. Pathogenic variants in the THRβ gene cause resistance to thyroid hormone, typically presenting with elevated thyroid hormone levels and thyroid gland enlargement. Despite receptor resistance, patients may develop, likely due to elevated T4 and T3 concentrations affecting the heart, where Thyroid hormone receptor alpha (THRα) is predominantly expressed. Recognizing thyroid hormone resistance is essential to avoid unnecessary treatment in asymptomatic cases.

Conflicts of Interest

The authors declare no conflicts of interest.

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Informed consent

Obtained from the patient.

Large Language Model

None

Authors Contribution

GK Conceptualization; case identification; writing original draft. HGA Case presentation: introduction; writing—original draft. NAA Discussion: writing original draft. AHA Corresponding author; review. All authors reviewed and approved the final manuscript.

Data Availability

All data supporting the findings of this study are included in the article. Additional information is available from the corresponding author upon reasonable request.

Declaration

This case was previously presented as a poster at the Endocrine Society Meeting 2024. Poster abstract link: here

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ASIDE Case Reports

Case Report

Management of Venous Thromboembolism in a Patient with Duplicated Inferior Vena Cava: A Case Report and Literature Review

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Interventional Cardiology

ABSTRACT

Anatomic variations of the inferior vena cava (IVC) are rare, occurring in less than 3% of the population, yet they can pose significant clinical and procedural challenges. We report the case of a 68-year-old male with a contraindication to anticoagulation due to gastrointestinal bleeding, in whom IVC filter placement was indicated for pulmonary embolism prophylaxis. During intra-procedural venography, the patient was found to have a duplicated inferior vena cava (DIVC), a rare vascular anomaly. Bilateral Denali filters were successfully deployed in both IVC limbs to ensure complete thromboembolic protection. This patient remains clinically stable at three-year follow-up with no recurrence of thromboembolism or filter-related complications. This case highlights the placement of bilateral filters in patients with DIVCs that do not converge below the renal veins. Recognizing this was crucial to ensure effective filter placement and avoid incomplete protection against embolism. This case underscores the importance of evaluating venous anomalies prior to interventional procedures involving the IVC. Failure to recognize such variations can lead to technical difficulties, procedural delays, or suboptimal outcomes, including persistent or recurrent thromboembolism. We also review the types of IVC anomalies, their embryology, and some of the potential complications they may cause. Careful procedural planning is essential for optimal patient management.

1. Introduction

Inferior Vena Cava develops from the regression and fusion of the embryonic postcardinal, subcardinal, and supracardinal veins. Anomalies in this process may result in duplication of the IVC [1, 2]. The most common anomaly is sub-renal IVC, with an incidence of 0.2-3% in the general population [3]. Morita further classifies inferior vena cava (IVC) anomalies into several types based on the presence and origin of interiliac venous communications. Type 1 refers to the azygos continuation of the IVC with normal drainage from both common iliac veins (CIVs). Type 2a represents double IVC without any interiliac connection. Type 2b involves a double IVC with an interiliac vein arising from the left CIV to the right IVC, while type 2c features a connection from the right CIV to the left IVC. Type 2d describes an interiliac vein originating from the left internal iliac vein (IIV) to the right IVC, and type 2e involves a connection from the right IIV to the left IVC. These distinctions are important for guiding surgical and interventional strategies [4]. In interventional procedures such as IVC filter placement or retroperitoneal surgeries, unrecognized anomalies can result in recurrent embolism, incomplete filter coverage, or intraoperative hemorrhage. Therefore, careful preoperative assessment and awareness of potential venous anomalies are essential to minimize these complications [5, 6, 7].

We present the case of a 68-year-old male in whom the incidental discovery of a duplicated inferior vena cava during management of gastrointestinal bleeding and recent pulmonary embolism highlights the importance of recognizing rare venous anomalies to guide appropriate intervention.

2. Case presentation

A 68-year-old male with a history of hyperlipidemia, hypertension, and recent pulmonary embolism presented for evaluation of melena and syncope. He had been initiated on apixaban three weeks prior following the diagnosis of a pulmonary embolism. In the days leading up to the presentation, he experienced progressive black, tarry stools and ultimately had a syncopal episode at home.

The patient was afebrile and denied chills, sore throat, nosebleeds, visual changes, cough, leg swelling, abdominal or urinary symptoms, joint pain, rash, numbness, or psychiatric concerns. They reported shortness of breath, chest pain, and a syncopal episode. Vital signs showed a heart rate of 108 bpm, RR 18, temp 98.4°F, and SpO_2 97% on room air. He was found to be hypotensive, and laboratory evaluation revealed a hemoglobin of 9 g/dL, significantly down from baseline.

D-dimers were elevated. X-ray chest was unremarkable; however, CT pulmonary angiography revealed a thrombus in the branch

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Table 1: Clinical Timeline of a Patient with Duplicated Inferior Vena Cava and Acute Venous Thromboembolism

Day	Clinical Summary
Day 1	Presented to ED with syncope and dyspnea; diagnosed with acute PE and bilateral DVTs. He started on apixaban (Eliquis) and was discharged in stable condition.
Day 18	Re-hospitalized due to copious hematemesis, raising concern for upper GI bleed. Anticoagulation was withheld considering suspected active GI bleeding.
Day 20	EGD revealed erosive gastritis without active bleeding. IR consulted for potential IVC filter placement due to anticoagulation contraindication.
Day 21	Digital subtraction venography showed duplicated IVC anatomy; bilateral Denali filters were placed in the infrarenal segments.
Day 22	Hemostasis confirmed; discharged in stable condition with filters placed for ongoing PE prophylaxis.

ED, Emergency Department; PE, Pulmonary Embolism; DVT, Deep Vein Thrombosis; GI, Gastrointestinal; EGD, Esophagogastroduodenoscopy; IR, Interventional Radiology; IVC, Inferior Vena Cava; IVCF, Inferior Vena Cava Filter; IV, Intravenous; PCP, Primary Care Provider.

of the pulmonary artery to the left lower lung lobe as shown in (**Figure 1**). Extensive bilateral thrombi were observed on performing Doppler venous ultrasound of the lower extremity, including femoral, popliteal, and posterior tibial veins of the left leg and common femoral, profunda femoris, femoral, and popliteal veins of the right leg. Anticoagulation was held, and he underwent esophagogastroduodenoscopy, which showed diffuse erosive and ulcerative esophagitis without evidence of active bleeding.

The patient started intravenous proton pump inhibitor therapy and later transitioned to oral pantoprazole. After initial stabilization, apixaban was resumed; however, the patient again developed hypotension and persistent decline in hemoglobin, requiring red blood cell transfusions. Antihypertensive medications were held. Due to concern for ongoing gastrointestinal bleeding and a contraindication to anticoagulation, interventional radiology was consulted for IVC filter placement. The procedure was performed under maximal sterile conditions with local anesthesia. The right common femoral venous access was obtained using ultrasound guidance and a micropuncture system. A 6 French sheath was placed, and a 5 French pigtail catheter was advanced. Digital subtraction venography revealed a duplicated inferior vena cava (IVC). A Denali filter was deployed in the infrarenal segment of the right IVC with satisfactory positioning and no significant tilt.

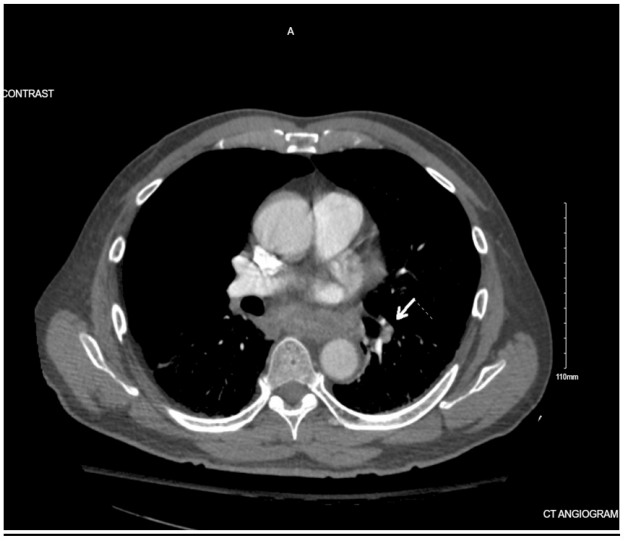

Figure 1: CT Angiogram showing Pulmonary Embolus in the intermediate branch of the pulmonary artery to the left lower lobe (White arrow)

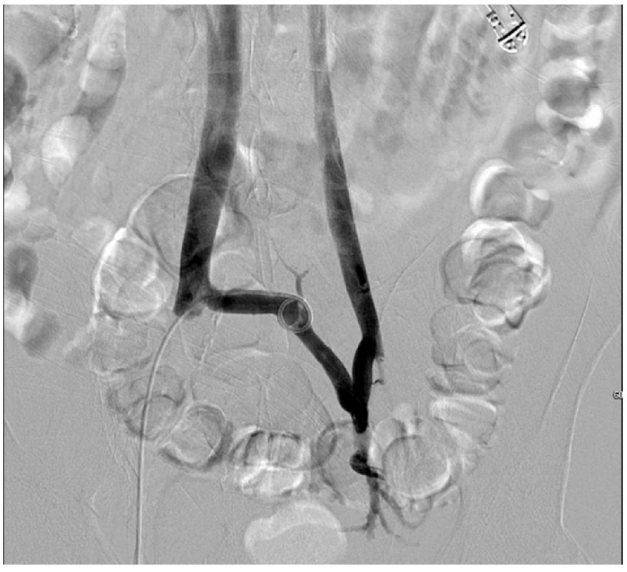

Figure 2: Venography showing duplicated IVC with bilateral filter placement. Morita Type 2b with interiliac communication arising from the left common iliac vein.

Subsequently, the left common femoral vein was accessed similarly. A 6-French sheath and pigtail catheter were used to perform digital subtraction venography, again demonstrating the duplicated IVC. A second Denali filter was deployed in the infrarenal left IVC with appropriate expansion and positioning. Hemostasis was achieved after removal of all devices. The diagnosis of duplicated IVC was made intra-procedurally, as no prior CT venography had been performed. On the other hand, the decision to place bilateral IVC filters as opposed to a unilateral filter was made because of the presence of bilateral DVTs. Also, Denali filters were selected for their retrievability and compatibility with small-caliber veins [8].

Following filter placement and permanent discontinuation of apixaban, the patient remained hemodynamically stable and experienced no further episodes of gastrointestinal bleeding. He was discharged in a stable condition with outpatient follow-up arranged with gastroenterology and primary care.

At follow-up, the patient presented with reported improved shortness of breath, and lower extremity ultrasound showed no thrombus. Repeat EGD revealed healing esophagitis, and he remained

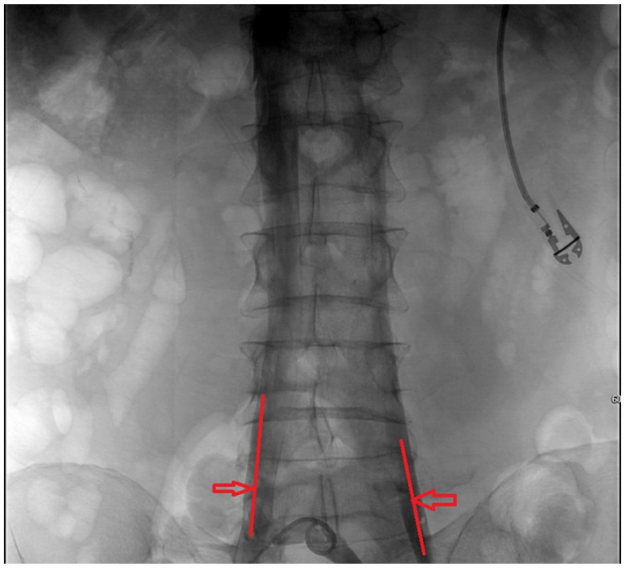

Figure 3: Fluoroscopy showing Bilateral IVCs with filter placement; red arrows indicate duplicated IVCs. Dual filters were placed because of the presence of bilateral DVTs and Morita Type 2b without infra-renal convergence. A single filter in the Right IVC would not be adequate in view of this anatomy.

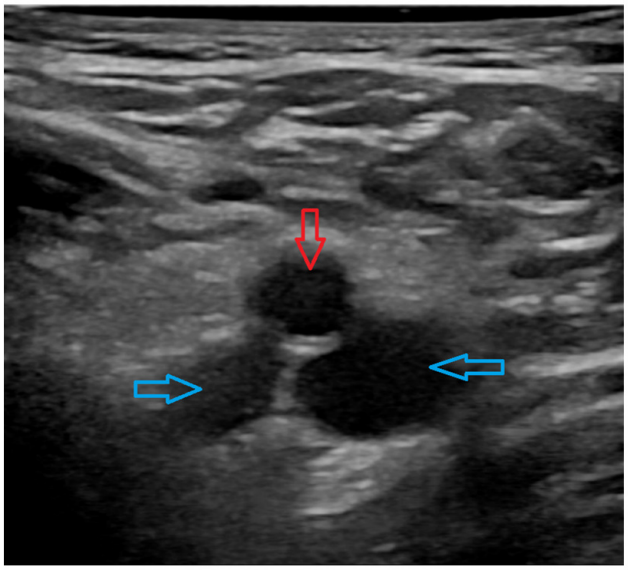

Figure 4: Ultrasound showing duplicated IVCs (blue arrows) and aorta (red arrow). The aorta has a more uniform, circular appearance, while IVCs have a more elliptical, collapsible appearance.

on pantoprazole. Due to recurrent unprovoked PEs, it was decided he needed lifelong anticoagulation. A trial of apixaban was once again attempted but was promptly discontinued after he developed hematemesis. At that time, IVC filters were left inside because of a high-risk history, but the patient was lost to medical follow-up afterwards. He presented to his PCP after about 3 years. He remains clinically stable with no recurrence of thromboembolism or filter-related complications.

3. Discussion

Double Inferior Vena Cava (DIVC) is a rare congenital vascular anomaly with an estimated incidence ranging from 0.2% to 3% [3, 2]. This condition arises due to incomplete regression of the embryonic venous system, specifically the right and left supracardinal veins. During embryological development, these venous structures typically fuse, forming a single IVC. However, when fusion fails to occur, two separate IVCs persist, often running on either side of the aorta and converging near the level of the renal veins. If this convergence does not result in a single venous trunk, a true double IVC develops [1, 3, 2] [9].

Duplicated inferior vena cava is classified into several types based on anatomical differences. In this case, the patient was found to have a duplicated inferior vena cava consistent with Morita type 2b anatomy, characterized by bilateral IVCs with an interiliac venous communication originating from the left common iliac vein (CIV) connecting to the right IVC [4].

In most cases, DIVC is asymptomatic and discovered incidentally, either on imaging or during surgical procedures [10]. Nevertheless, it can carry significant clinical implications, particularly in the context of venous thromboembolism (VTE) and interventional procedures such as IVC filter placement. If a left-sided IVC is unrecognized, it may drain via collaterals into the azygous system, which can bypass a unilaterally placed IVC filter, leading to recurrence, as illustrated in a case report by Malgor et al and others [11, 5, 6, 7].

The 2020 clinical practice guideline by the Society of Interventional Radiology recommends bilateral filter placement in patients with duplicated inferior vena cava (IVC) when the two limbs do not converge below the renal veins, as in our case. This is because placing a filter in only one limb may leave the other venous channel unprotected, allowing thrombus to bypass the filter and reach the pulmonary circulation, supporting bilateral filter placement in our case. The guideline highlights that without bilateral protection, there is a significant risk of recurrent embolic events due to incomplete filtration, making recognition of this anatomical variant essential for effective venous thromboembolism prevention [12].

Selection of the optimal filter strategy should be individualized, considering anatomical details, the relative size of each IVC, and the location and pattern of confluence. Recent case reports emphasize the utility of pre-procedural venography to delineate venous anatomy, guide decision-making, and ensure optimal outcomes [13].

We conducted a review of the literature and identified several case reports that describe various strategies for filter placement in the setting of DIVC. These include placement of a single filter above the confluence of the bilateral IVCs, placement of two separate filters, one in each IVC below the renal veins, or placement of a filter in the dominant IVC, meaning the vessel carrying most of the venous return from the lower extremities. These approaches are summarized in **(Table 2)** [10, 9, 14, 13, 15, 5, 16, 17, 18, 19, 20]. Accurate diagnosis of DIVC relies on imaging, with computed tomography (CT) and venography being the most reliable modalities. These not only confirm the presence of dual IVCs but also clarify their anatomical course and their relationship with adjacent structures such as the renal veins [21].

Importantly, DIVC can pose challenges in retroperitoneal surgery, renal transplantation, and other vascular interventions due to the risk of unexpected hemorrhage or inadvertent injury to anomalous vessels [22, 23, 6, 7]. For example, Habuchi et al. described a

Table 2: Case reports with IVC filter placement in patients with duplicated IVCs

Case number	Reference	Number of Filters	Location
1	Hatmi et al. [10]	1	Suprarenal
2	Lan et al. [13]	1	Left IVC (the culprit vein)
3	Sartori et al. [18]	2	Both IVC
4	Malgor et al. [5]	2	Both IVC
5	Malgor et al. [5]	2	Initially only main IVC. Later, due to recurrent PE, the Left IVC was also discovered on repeat imaging, and a filter was placed there as well.
6	Sinnott et al. [19]	2	Both IVC
7	Lagrotta et al. [14]	1	Right Infrarenal IVC
8	Balawender et al. [9]	2	Both IVC
9	Li et al. [15]	1	Right IVC
10	Li et al. [15]	1	Suprarenal above confluence
11	Oppenheim et al. [16]	2	Both
12	Suzuki et al. [20]	2	Both
13	Patel et al. [17]	2	Both (infrarenal)

IVC, Inferior Vena Cava; PE, Pulmonary Embolism; Suprarenal, above the renal veins; Infrarenal, below the renal veins.

case of renal cell carcinoma that involved the left-sided IVC, necessitating surgical excision of the vessel [24]. Similarly, Wang et al. reported a case in which DIVC caused ureteral obstruction, highlighting the need to consider this anomaly in the differential diagnosis of extrinsic ureteral compression [25]. Given these potential complications, awareness of DIVC is crucial in preoperative planning for retroperitoneal surgeries, and necessary intraoperative adaptations should be made when this vascular variant is present [26]. No specific inferior vena cava (IVC) filter brand is considered universally superior or "the best" according to current clinical guidelines or comparative studies. The American College of Radiology states that multiple retrievable filter designs are available in the United States, with no one design currently considered superior, and device selection should be individualized based on patient anatomy and clinical scenario.[27] Similarly, the National Comprehensive Cancer Network notes that, due to a lack of randomized controlled trials comparing filter types, no particular filter should be considered superior [28].

Comparative studies show that the Denali filter demonstrates favorable technical performance relative to other commonly used retrievable filters. Denali is associated with lower rates of filter tilt and strut penetration compared to Celect and Option filters, as well as shorter fluoroscopy times and lower rates of complex retrievals. For example, Denali had a significantly lower retrieval failure rate and required less use of advanced retrieval techniques than Option and Tulip filters. In prospective multicenter data, Denali exhibited high technical success for both placement and retrieval, with low complication rates and no filter fractures or significant tilt at retrieval [8][29][30, 31, 32].

In summary, no IVC filter brand is considered superior or the best by major guidelines. Still, Denali consistently demonstrates lower complication rates and easier retrieval compared to several other retrievable filters in head-to-head studies.

Though retrievable filters are preferred to minimize long-term complications such as IVC occlusion, many remain in place due to persistent contraindications to anticoagulation, as in this case [12].

4. Conclusion

Duplicated inferior vena cava, a rare congenital vascular anomaly, has vast clinical implications, particularly in patients who require IVC filter placement. In this case, the anatomical variant was incidentally discovered during emergent filter deployment in a patient with active gastrointestinal bleeding and recent pulmonary embolism on anticoagulation. Bilateral filter placement was necessary to ensure complete venous thromboembolic protection.

Limitations of this report include the absence of pre-procedural CT venography, lack of anatomical detail such as confluence level and IVC diameters, and no attempt at filter retrieval, which could have impacted long-term outcomes. Also, this study could not determine procedural costs and radiation exposure. This case underscores the importance of procedural vigilance and the need for interventionalists to be familiar with venous anomalies to prevent inadequate treatment or complications. If unrecognized, duplicated IVC can lead to incomplete filter coverage, placing patients at continued risk for pulmonary embolism in the setting of deep vein thrombosis. Early recognition and individualized filter strategy in DIVC are essential for procedural success and avoiding recurrent embolism in high-risk, anticoagulation-intolerant patients.

Conflicts of Interest

The authors declare that they have no competing interests.

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Informed consent

Consent for publication was obtained from the patient involved in this case report.

Large Language Model

None

Authors Contribution

AJ and ZE contributed to conceptualization, data curation, investigation, resources, writing – original draft, writing – review and editing, visualization, and project administration. FR contributed to writing, including review, editing, and proofreading.

Data Availability

This is a case report. No datasets were generated or analyzed during the preparation of this manuscript. All relevant clinical information has been included within the article itself.

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