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Case Report

Benign Pheochromocytoma Coming Back with Bony Metastasis: A Case Report and Literature Review

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ABSTRACT

Pheochromocytoma is an uncommon adrenal medulla tumor that secretes catecholamines. It is usually a benign condition and is generally treated with adrenalectomy; in a small proportion of cases, however, it might return or spread. Pheochromocytoma is uncommon to recur or metastasize, meaning every reported case is clinically relevant.

A 46-year-old Caucasian woman initially presented with conventional catecholamine excess symptoms—refractory hypertension, palpitations, diaphoresis, and headaches. Imaging showed a sizable right adrenal mass; biochemical testing indicated very high plasma metanephrines. A medical decision was made to perform a right adrenalectomy; pathology confirmed a benign pheochromocytoma. After surgery, her symptoms went away, but she was missed for follow-up. Four years later, she came back with comparable symptoms; biochemical screening found increased metanephrines once more, and a computed tomography (CT) scan revealed local recurrence in the right adrenal bed. Notably, the CT also disclosed a lytic lesion in a lumbar vertebra and evidence of bone metastases from the pheochromocytoma. This instance highlights a rare situation in which a pheochromocytoma, initially thought to be innocuous, reoccurred with distant skeletal involvement.

In conclusion, a very rare, recurrent pheochromocytoma with bone metastases underscores the importance of continuous monitoring even after complete tumor removal. Early recognition of metastasis or relapse can significantly impact therapy and outcomes. This case highlights the necessity of ongoing follow-up in patients with pheochromocytoma and alerts individuals to potential late metastatic symptoms.

1. Introduction

Pheochromocytomas are rare neuroendocrine malignancies originating from chromaffin cells of the adrenal medulla. Usually benign, but 10% are approximately malignant; the incidence of malignancy is 2.5%-13% [1]. No clear histopathological standards differentiate benign from malignant neoplasms at the time of initial diagnosis. Malignant pheochromocytomas usually metastasize to the bone, kidney, lymph nodes, and lung and rarely to the brain, prostate, skin, and urinary bladder. Although bone is the commonest site for metastases, vertebral involvement is rare [2] . Pheochromocytomas exhibit symptoms of catecholamine excess, including headaches, paroxysmal hypertension, palpitations, flushing, and sweating. However, a small percentage show malignant behavior, determined by local recurrence or distal metastases; many times, these tumors are benign and surgically excised; that is, adrenalectomy is curable. Though rare, estimated in approximately 10–14% of patients, pheochromocytoma recurs years or even decades after the first therapy following curative surgery. Long-term follow-up is necessary because of the possibility of recurrence or metastasis, even in tumors initially deemed "benign. " This case report has clinical importance since it describes a patient with a pheochromocytoma first handled as a benign tumor who later showed recurrence with bone metastases. Such a presentation highlights gaps in our ability to accurately forecast tumor behavior, which is uncommon.

2. Case presentation

Patient Details: A 46-year-old Caucasian female with long-standing insulin-dependent diabetes mellitus and a history of poorly controlled hypertension on several antihypertensive drugs including Hydrochlorthiazide 25 mg daily (started as first line at the time of diagnosis), Losartan 100 mg daily (added on when diagnosed with diabetes), Amlodipine 10 mg daily, and Hydralazine 50 mg tid. Presented to the emergency department with extreme weariness, ongoing upper abdominal discomfort, and undesired weight loss. She also noted sporadic heart pounding, chest heaviness, profuse perspiration, face flushing, and severe headaches over the past few weeks. Her vital signs during presentation were as follows: blood

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pressure, 186/104 mmHg; heart rate, 110 beats per minute; respiratory rate, 18 breaths per minute; temperature, 36.8°C; and oxygen saturation, 98%. No known family history of pheochromocytoma or other endocrine tumors existed. Physical examination showed persistent hypertension and facial flushing but was otherwise normal for the initial appearance and diagnostic work-up. Differential diagnosis considered for these signs and symptoms included: hypertensive urgency, acute coronary syndrome, perimenopause, hyperthyroidism. Abdominal CT scan was ordered to investigate the cause of abdominal pain, and it revealed an adrenal mass. Subsequently, a diagnosis of pheochromocytoma was considered.

Biochemical testing confirmed a hypercatecholaminergic state by revealing remarkably high plasma-free metanephrine levels (>13,000 pg/mL; normal <200 pg/mL). TSH hormone level was ordered to exclude hyperthyroidism and was within normal range. Her set of symptoms led one to consider a catecholamine-secreting tumor.

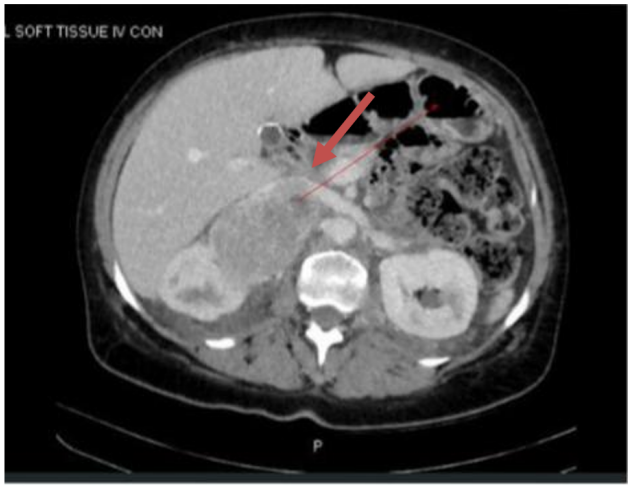

Figure 1: CT showing large right adrenal tumour nearly 12 cm in size – at the time of initial phaeochromocytoma diagnosis.

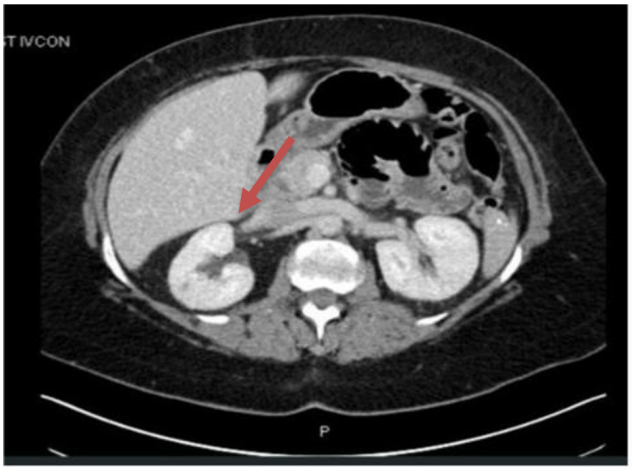

Figure 2: Follow-up CT status post resection of right adrenal phaeochromocytoma, showing complete resection of the mass.

An abdominal CT scan was done for tumor localization; it showed a vast right adrenal mass measuring around 12 cm in size. On preliminary CT abdomen, the big right adrenal tumor compressing nearby structures **(Figure 1)** shows no evident metastatic lesions. Based on the imaging, biochemical evidence, and clinical picture, a right adrenal pheochromocytoma was diagnosed. Initial therapy and results: The patient underwent an open right adrenalectomy **(Figure 2)** following suitable preoperative Doxazosin initially started at 1 mg bid three weeks prior to surgery and titrated up to 8 mg bid, and then metoprolol 50 mg bid started 3 days before surgery. Post-surgery antihypertensive Hydralazine was stopped immediately. Histopathology confirmed a pheochromocytoma restricted to the adrenal gland with no cancerous characteristics discovered; the resected tumor was well-encapsulated. Surgical borders were well-defined, with no infiltration into adjacent tissues. At the time, no adjuvant therapy was advised. Postoperative follow-up biochemical tests revealed normalized plasma metanephrines, and the patient's symptoms resolved completely; her blood pressure also improved, allowing a reduction in antihypertensive medication. Though, unfortunately, she was lost to follow-up following surgery and did not have scheduled monitoring, she was counseled on continuous monitoring with periodic biochemical testing and imaging.

Around four years following the first adrenalectomy, the patient reappeared with a recurrence of symptoms. Reminiscent of her original presentation, she reported new episodes of palpitations, sweating, facial flushing, and elevated blood pressure levels. Clinicians swiftly requested further biochemical testing and imaging, knowing the possibility of tumor recurrence. Biochemical test results showed that (3,500 pg/mL) were plasma metanephrine levels. A contrast-enhanced CT scan of the stomach strongly indicated loco-regional recurrence of pheochromocytoma in the adrenal bed since it revealed several irregular soft tissue masses (approximately 2x4 cm each) in the right retroperitoneum close to the site of the previous adrenalectomy. Notably, the CT scan also found a solitary lytic lesion in the body of the L2 vertebra, thereby generating suspicion of a metastatic deposit from the pheochromocytoma **(Figure 3)**. CT scan at recurrence showed a recurrent tumor mass in the right adrenal bed and a lytic destructive lesion in the L2 vertebral body consistent with metastatic spread. Magnetic Resonance Imaging revealed no apparent liver, lungs, or other organ lesions. Later, a whole-body radionuclide investigation, metaiodobenzylguanidine scan, or PET scan was planned to confirm the adrenergic character of the spinal lesion. In this instance, the clinical setting indicated that the vertebral lesion was a metastasis of the pheochromocytoma; therefore, the tumor was classified as malignant. The patient's situation was addressed at a multidisciplinary cancer board. Given the loco-regional recurrence and solitary bone metastasis, a combined treatment approach was intended. The patient was put under alpha- and beta-adrenergic blockage to help her stabilize her cardiovascular condition. She then had surgical excision of the recurring retroperitoneal tumor masses. Options for treating vertebral metastasis included surgical stabilization, radiation treatment, or targeted radionuclide therapy (e.g., I-131 MIBG or peptide receptor radionuclide therapy). Ultimately, localized radiation therapy was performed on the L2 vertebra to control the metastatic lesion and avoid spinal cord compression. Biochemical metanephrine levels after treatment revealed a notable decrease, and the patient's symptoms improved. The patient was set for close long-term follow-up every six to twelve months with intermittent biochemical monitoring and imaging.

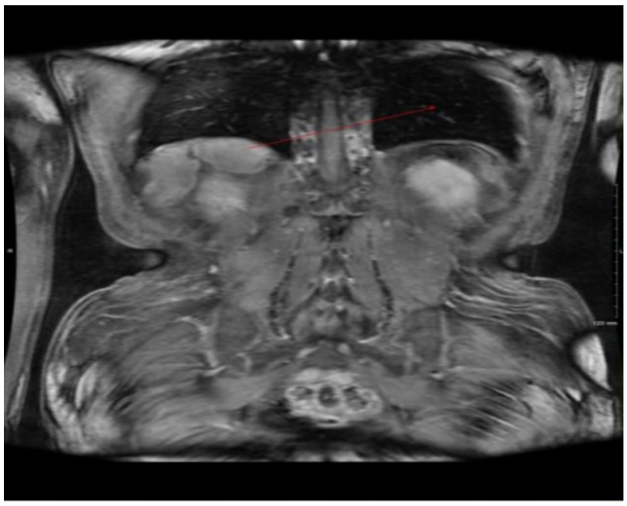

Figure 3: CT coronal section showing soft tissue nodules in the right posterior pararenal space suspicious for recurrent phaeochromocytoma.

3. Discussion

Pheochromocytoma is a rare tumor that arises from the chromaffin cells of the adrenal gland. The annual incidence of pheochromocytoma is less than 1 per 100,000 people [3] and the prevalence is 1 in 6500 [4]. The usual peak age of diagnosis is the third to fifth decade of life, with equal incidence in men and women [5]. Most pheochromocytomas are sporadic, but about 40% of the pheochromocytomas are familial, associated with genetic mutations [4, 6]. VHL (von Hippel-Lindau, vHL), NF1 (Neurofibromatosis Type 1, NF1), and RET (Multiple Endocrine Neoplasia Type 2, MEN 2) are the common mutations associated with pheochromocytoma [7]. Approximately 10% of all pheochromocytomas are malignant [3]. About 50% of the patients with metastatic disease have germline mutations [8]. The five-year survival rate is about 90% in benign pheochromocytoma and about 40% in malignant pheochromocytoma [3]. Mortality and morbidity are related to the mass effect and the high catecholamine burden leading to hypertension, arrhythmias, cardiomyopathy, stroke, and even death [7]. Male sex is associated with higher mortality [9]. Because of their broad and nonspecific clinical symptoms, pheochromocytomas are often referred to in medicine as "the great mimicker. " Although pheochromocytomas can sometimes present atypically or even be found incidentally, this patient's initial presentation—hypertension, headaches, perspiration, palpitations—is typical. Orthostatic hypotension and syncope are seen in some patients [10]. Diagnosis begins with biochemical confirmation of catecholamine excess [11] (increased plasma or urinary metanephrines), then imaging to locate the tumor. Genetic testing should be considered in all patients [12].

Complete surgical resection (adrenalectomy) is the ultimate therapy for localized disease and usually results in a cure for benign tumors. Minimally invasive adrenalectomy is preferred in most patients, while open resection is reserved for patients with large (>6cm) or invasive tumors to prevent tumor rupture and local recurrence [12]. The tumor should be pathologically confirmed for the absence of malignancy, even though histopathological features do not reliably distinguish between benign and malignant pheochromocytomas [13]. Post-operatively, biochemical testing should be done regularly to confirm complete resection [14].

Initial care for our patient followed these principles and appeared effective, as evidenced by normalized laboratory results post-surgery and symptom resolution. Though the best first treatment is in place, a small number of patients can experience tumor recurrence. Reported recurrence rates of pheochromocytoma following adrenalectomy range between 6% and 16% in several series. One long-term study found recurrence in up to 10–14% [14] of cases. Recurrence in our patient four years after this window falls. In this instance, a lack of routine follow-up postponed the detection of recurrence until it became symptomatic. This highlights a major difficulty: patients might become non-adherent to follow-up after the first tumor is eliminated and symptoms subside, therefore missing an early diagnosis of recurrence.

Especially for those with bigger tumors, hereditary syndromes, or any other risk factors, lifelong surveillance with yearly or bi-yearly biochemical testing and frequent imaging is often advised to detect recurrence at a treatable level. The malignant potential of pheochromocytomas is another important point demonstrated by this case. There are no predictive criteria for the recurrence of pheochromocytoma. As per one study, patients with primary tumor size >5cm and average Ki-67 counts >3% are at higher risk of recurrence [15].

Recurrence is associated with multiple node involvement and distant metastasis and, therefore, is difficult to treat with surgery alone [15]. The recurrence time is variable, ranging from 1 year after surgery to decades later, but is usually observed after 2-3 years. Therefore, lifelong follow-up is recommended to detect recurrence or metastasis [16]. Annual follow-up should be preferred in patients with familial, large, or bilateral tumors, while biennial follow-up might be adequate for low-risk risk [17]. Malignancy in pheochromocytoma is characterized by metastases to areas where chromaffin tissue is typically absent (e.g., bones, lungs, liver, and distant lymph nodes). Malicious behavior is observed in approximately 10% of pheochromocytomas (or slightly higher in some recent studies). No completely trustworthy histological standards predict malignancy: characteristics like cellular atypia or further adrenal extension do not definitively indicate that a pheochromocytoma will metastasize.

In reality, the only certain indicator of cancer is the documentation of metastatic spread. Though the subsequent appearance of a bone lesion showed its cancerous nature, in our patient's first operation, the tumor was reported as "benign," indicating no invasion or metastasis was apparent at that moment. This case emphasizes the diagnostic difficulty that even a tumor designated benign may have malignant potential that is only discovered over time. Although some research has attempted to identify predictors of aggressive behavior (such as tumor size exceeding 5 cm, a high cellular proliferation index (like Ki-67) greater than 3%, or specific genetic mutations), these findings are inconclusive.

In pheochromocytomas, genetic testing is crucial; up to 40% are associated with germline mutations (e.g., VHL, RET, NF1, SDHB/D). Malignant cases are more likely to have underlying mutations (about half of metastatic pheochromocytomas show hereditary mutations). Although no genetic testing was initially performed in our case, it would be wise to check for changes like SDHB (which is frequently associated with aggressive, metastatic pheochromocytoma), given the tumor's behavior. Bone metastasis in pheochromocytoma is a noteworthy finding, as shown in this patient. Among metastatic pheochromocytomas, bone is indeed one of the most common locations of dissemination. Research indicates that bone involvement occurs in approximately 60–70% of malignant cases. Patients with bone metastases may show bone

pain, pathological fractures, or neurological symptoms if the spine is affected [18].

The discovery of a single bone metastasis presented significant management issues. While loco-regional recurrence can usually be managed with multiple surgeries, disseminated disease may require systemic treatment. For the recurrent adrenal lesion, this patient's treatment comprised surgery and radiation for the bony metastasis. Other or supplemental treatments for metastatic pheochromocytoma include targeted radiotherapy using radioactive iodine-labeled MIBG [19] and systemic chemotherapy (including cyclophosphamide-based regimens [20]. Every strategy must be tailored to the patient's tumor biology and the extent of the disease. Our case highlights how even "benign" pheochromocytomas can behave aggressively and underscores the importance of a multidisciplinary approach when they do.

Comparing this case to the current literature, it fits with other studies stressing the unpredictability of Pheochromocytoma recurrence. Recurrence has been noted several years after resection; a few pheochromocytomas were initially non-metastatic, but then developed distant metastases, including skeletal lesions. The clinical result can vary: while some patients respond well to additional therapies and second surgeries, others may have a more aggressive course. Prognostically, benign pheochromocytomas have a high 5-year survival (90%), whereas malignant pheochromocytomas have a poorer prognosis (5-year survival often around 40–50%, heavily dependent on the extent of metastasis and effectiveness of therapy). Early detection of recurrence, as in the case of our patient, once she sought medical care, likely increases the chances of a good outcome by enabling prompt action. This case helps to advance the field of knowledge by highlighting a rare instance of repeated pheochromocytoma with bone metastasis. This case report emphasizes three important ideas: the need for ongoing follow-up, the potential for metastases to develop even after curative surgery, and the importance of physicians being alert for signs of recurrence. It also emphasizes the need for more studies on predictive indicators of malignancy and relapse in pheochromocytoma, which might finally inform early interventions and surveillance strategies for high-risk individuals.

4. Conclusion

Though rare, recurrent pheochromocytoma with far-off metastases is a vital clinical entity. This case illustrates the importance of lifetime monitoring, demonstrating how pheochromocytomas, initially treated as benign tumors, can recur years later with malignant characteristics. For doctors, it is important to keep a high index of suspicion for recurrence in any patient with a history of pheochromocytoma exhibiting suspicious symptoms, even many years following surgical resection. Early detection of recurrence or metastasis enables quick, aggressive treatment that can improve patient outcomes. To find late recurrences or metastases, thorough long-term follow-up is required. A multidisciplinary approach is recommended to manage these uncommon but life-threatening incidents; even "benign" pheochromocytomas are not entirely benign.

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

FM analyzed and interpreted the patient data and provided critical revisions to the manuscript. AG reviewed and provided critical revisions to the manuscript. TZ was a major contributor to writing the manuscript. EA contributed to writing the manuscript. SM contributed to writing the manuscript.

Data Availability

The datasets generated and/or analyzed during the current study are included in the published article. Additional data related to this study are not publicly available but can be obtained upon request from the corresponding author.

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Case Report

Bone Marrow Necrosis in A Male Patient with Anti-Phospholipid Syndrome: A Case Report with Literature Review

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ABSTRACT

Anti-phospholipid syndrome (APS) is a systemic autoimmune disease causing arterial and venous thrombosis, leading to macrovascular and microvascular complications. Bone marrow necrosis (BMN) is defined as the death of hematopoietic tissue and the loss of fat cells in a bone marrow biopsy. BMN is typically associated with a poor prognosis, with most patients dying within weeks. We present a case of BMN in a 32-year-old male patient with APS admitted to our hospital. The patient presented with bilateral non-healing leg ulcers and bilateral lower limb edema. The findings of the duplex ultrasound were consistent with old bilateral deep vein thromboses in the calves. The presence of acute kidney injury and proteinuria prompted a renal biopsy, which revealed chronic thrombotic microangiopathy. Bone marrow biopsy revealed BMN. Unfortunately, the patient did not respond to immunosuppressive treatment and passed away due to septic shock. The unique features in the patient's presentation, combined with the availability of extensive data on the patient's history and investigations, further enhance its significance. It is not possible to establish a cause-and-effect relationship or draw conclusive findings from this case report alone. More case reports from clinicians who come across BMN in patients with APS are needed to broaden our understanding of the pathogenesis, presentation, management, and outcomes.

1. Introduction

Anti-phospholipid syndrome (APS) is a systemic autoimmune disease causing arterial and venous thrombosis, leading to macrovascular and microvascular complications [1, 2]. Notably, APS also leads to pregnancy morbidity, including spontaneous abortions, preeclampsia, fetal distress, and placental insufficiency [3]. The estimated prevalence of APS is 40 to 50 cases per 100,000 people [4]. This syndrome is well-known for being more prevalent among females, with a female: male ratio of 3.5:1 [2]. The pathogenesis is primarily mediated by auto-antibodies – namely, lupus anticoagulant, anti-cardiolipin, and/or anti-β2GPI antibodies [3]. The etiology may be primary isolated APS or secondary to another autoimmune disease, most commonly systemic lupus erythematosus (SLE) [3]. APS diagnosis requires the presence of clinical evidence of thrombosis or pregnancy morbidity, as well as laboratory evidence of persistently elevated titers of the previously mentioned antibodies [5]. Although thrombosis can occur anywhere, deep vein thrombosis (DVT) of the lower limbs is the most common presentation of venous thrombi [3]. Cerebral venous thrombosis is another less common manifestation [4]. Arterial thrombosis most commonly presents as transient ischemic attacks (TIAs) and ischemic strokes [3, 4]. In addition, manifestations of microvascular thrombosis can also occur, most commonly affecting the skin and the kidneys [4]. Management is primarily focused on preventing thrombosis [6]. Primary prevention with low-dose aspirin is recommended for patients with a high-risk antiphospholipid profile [7]. Secondary prevention in patients with APS and a history of venous thrombosis typically involves the use of warfarin or direct oral anticoagulants (DOACs) [7]. Meanwhile, in accordance with the recommendations of the 16th International Congress on Antiphospholipid Antibodies, secondary prevention in patients with APS and a history of arterial thrombosis is either low-dose aspirin plus standard-intensity warfarin (INR range, 2 to 3) or warfarin at an INR > 3 [7]. The use of DOACs is typically limited to those who can't tolerate warfarin or those with features of low-risk disease [7].

Bone marrow necrosis (BMN) is defined as the death of hematopoietic tissue and the loss of fat cells on bone marrow biopsy [8]. This rare entity is not only easily overlooked, but it must also be carefully distinguished from other bone marrow pathologies [8]. Underlying etiologies of BMN include hematological malignancies, infections, sickle cell disease, disseminated intravascular coagulation (DIC), and radiation [9, 8, 10]. Although the exact pathogenesis remains poorly understood, it is hypothesized that thrombi or emboli leading to hypoxemia is the mechanism underlying BMN [9, 8]. The clinical manifestations associated with BMN include bone pain,

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fever, and cytopenias – all of which are non-specific, further complicating diagnosis [8]. BMN is typically associated with a poor prognosis, with most patients dying within weeks [11, 9, 8].

BMN is an exceedingly rare complication of APS, with only two previously reported cases in the literature [12, 13]. We present a case of BMN encountered in a male patient with APS at our hospital.

2. Case presentation

A 32-year-old male patient presented with a two-month history of recurring attacks of fever, headache, and easy fatigability. As well as a one-month history of hypertension and bilateral painful non-healing leg ulcers. His medical history revealed left calf DVT, pulmonary embolism, and myocardial infarction three years prior to presentation. At that time, the patient was started on warfarin for a few months, then shifted to apixaban. Two months later, he developed recurrent left calf DVT two years before presentation, then bilateral calf DVTs one year prior to presentation. His past medical history was otherwise unremarkable. He has a positive family history featuring a father who developed DVT, and a sister who experienced DVT and an abortion, neither of whom was tested for APS or other autoimmune conditions. Upon presentation, physical examination revealed bilateral lower limb edema and bilateral leg ulcers. The ulcers were irregular, non-bleeding, with well-defined borders, and located in the gaiter area. Laboratory investigations at the time of admission revealed normocytic normochromic anemia, thrombocytopenia, and acute kidney injury (AKI). TTP was excluded based on normal bilirubin levels, normal LDH levels, a normal reticulocyte count, and the absence of schistocytes in the peripheral blood. More details on the lab investigations at the time of admission can be found in **(Table 1)** and **(Table 2)**.

Consequently, ultrasound abdomen and pelvis revealed an enlarged right lobe of liver measuring 18 cm with an echogenic pattern. Additionally, bilateral grade I nephropathy was detected. The nephrology unit recommended renal biopsy, which showed chronic thrombotic microangiopathy (CTMA), characterized by arteriolar thrombosis with marked mucinous intimal degeneration and fibrinoid necrosis. One glomerulus exhibited global necrosis, diffuse moderate interstitial fibrosis, and tubular atrophy of 40%. Diffuse moderate acute tubular necrosis with RBC casts was also observed.

Furthermore, bone marrow aspiration (BMA) revealed diluted aspirate containing only a small number of cells, including mature granulocytes, segmented neutrophils, mature lymphocytes, a few normoblasts, and occasional megakaryocytes. Blast cells were 1% and plasma cells were 0%.

Thrombophilia workup showed positivity for lupus anticoagulant, anti-cardiolipin antibodies, and anti-β2GPI antibodies, consistent with triple-positive APS. Antibody levels were considered to fall within the moderate-positive titers classification. This was repeated 12 weeks later to confirm the persistent elevation in antibodies. Further details on the thrombophilia work-up can be found in **(Table 3)**. SLE was excluded based on negative antinuclear antibody (ANA), negative anti-double-stranded deoxyribonucleic acid (dsDNA) antibody, and normal C3 and C4 levels. Duplex ultrasound of the bilateral lower limbs showed the majority of the veins to be non-compressible over an iso-echoic thrombus with central canalization, consistent with the presence of old DVTs. A virology panel for hepatitis C, hepatitis B, and HIV was all negative.

Table 1: Lab investigations of the patient at the time of admission

Parameter	Result	Reference range
Hemoglobin	9.7 g/dL	(13 – 17)
Hematocrit	29.2 %	(40 – 52)
Mean Corpuscular Volume	78.1 fL	(76 – 96)
Mean Corpuscular Hemoglobin	26.1 pg	(26 – 32)
Mean Corpuscular Hemoglobin Concentration	33.2 g/dL	(33 – 37)
Red blood cells	3.74×10^6/uL	(4.5 – 5.9)
Platelets count	15×10^3/uL	(150 – 450)
White Blood Cell	5.2×10^3/uL	(4 - 11)
Basophil	0 %	(0 – 1)
Eosinophil	0 %	(1 – 6)
Neutrophil	67.0 %	(40 – 70)
Lymphocyte	24 %	(20 – 45)
Monocyte	9 %	(2 – 8)
Urea	113 mg/dL	(15 – 45)
Serum creatinine	2.5 mg/dL	(0.7 – 1.4)
Albumin-creatinine ratio	1233	(< 70)
Glomerular filtration rate	46 mL/min/1.73 m^2	(> 90)
Cystatin C	1.68 mg/dL	(0.71 – 1.21)
Total serum bilirubin	0.6 mg/dL	(0.3 – 1.2)
Direct serum bilirubin	0.15 mg/dL	(0.1 – 0.3)
Lactate dehydrogenase	200 units	(135 – 225)
Prothrombin time	13.3 seconds	(11.3 – 13.2)
International normalized ratio	1.18	
Partial thromboplastin time	53.5 seconds	(Up to 40)

Table 2: Urine analysis findings

Parameter	Result	Reference range
Pus cells	2–4	(0 – 5)
Red blood cells	50–60	(0 – 3)
Hyaline casts	Present	None
Dysmorphic RBCs	Absent	None
Urinary protein	163 mg/dL	
Urinary creatinine	39 mg/dL	
Protein-to-creatinine ratio	4.12	(Up to 0.2)

The patient was administered hydroxychloroquine 200 mg twice daily, prednisolone 20 mg once daily, and cyclophosphamide 600 mg IV once weekly for two weeks, then 50 mg twice daily for two months. Regrettably, the patient did not respond to these treatments and subsequently complained of dizziness and fatigue. CBC revealed an alarming hemoglobin level of 5.7 g/dL and a WBC count of 4.7 × 103/mm3.

Consequently, the patient underwent bone marrow biopsy two months after presentation, which showed extensive areas of bone marrow necrosis (BMN) with a few apoptotic cells (Figure 1).

Table 3: Thrombophilia work-up

Parameter	Result	Reference range
PCR for factor V Leiden	Positive for heterozygosity (R506Q)	
PCR for MTHFR gene mutation	Positive for homozygosity (C677T)	
PCR for prothrombin gene mutation	Negative	
Protein C	111.0 %	70 - 140
Protein S	101.8 %	59 - 118
Antithrombin III	97.6 %	70 - 125
Lupus anti-coagulant	3.5	Negative: 0.8 – 1.2
		Weak positive: 1.2 -1.5
		Moderate positive: 1.5 – 2.0
		Strong positive: > 2.0
Anti-cardiolipin IgG	39.8 U/ml	(Up to 10)
Anti-cardiolipin IgM	2.2 U/ml	(Up to 7)
B2 glycoprotein IgG	16.5 U/ml	Negative: < 5
		Equivocal: 5- 8
		Positive: > 8
B2 glycoprotein IgM	1.7 U/ml	Negative: < 5
		Equivocal: 5- 8
		Positive: > 8

MTHFR, methylene tetrahydrofolate reductase

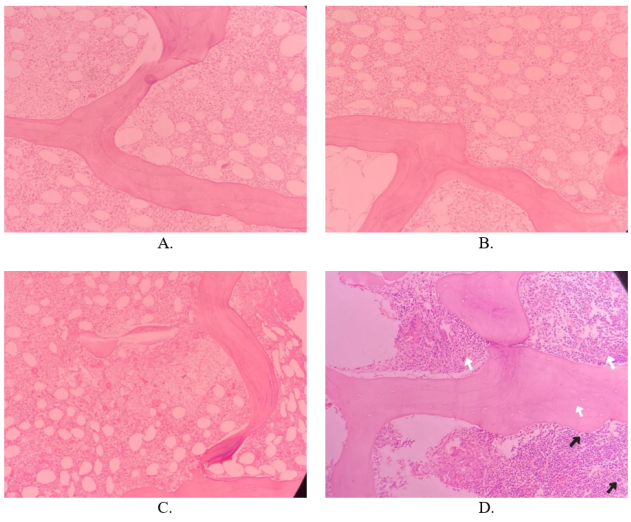

Figure 1: Bone marrow biopsy showing bone marrow necrosis.
Images A-C show several intratrabecular spaces showing bone marrow necrosis characterized by loss of cellular details with indistinct cellular borders and nuclear pyknosis with deposition of eosinophilic amorphous debris. In image D, the white arrows point to intertrabecular spaces with erythroid and granulocytic hyperplasia and few megakaryocytes, and the black arrows point to megakaryocytes.

Intratrabecular hematopoietic spaces were preserved, exhibiting erythroid and granulocytic hyperplasia. Bone marrow sections also demonstrated multiple small granulomas. Subsequently, the patient was administered pulse dexamethasone and rituximab 375 mg/m2 weekly for four doses. Unfortunately, the patient passed away as a result of septic shock secondary to pneumonia. This came four months after the initiation of immunosuppressive therapy and two months after being diagnosed with BMN.

3. Discussion

To the best of our knowledge, this is only the third case in the literature of BMN in APS, highlighting the rarity of this presentation. Interestingly, the two previous case reports were published in 1995 and 1997 [12, 13]. This case report is published more than 25 years later, further underscores its significance. This male patient with a history of recurrent arterial and venous thromboembolism presented to our hospital with painful non-healing ulcers and bilateral lower limb edema. Thrombophilia work-up was consistent with APS, which was further supported by a positive family history. Upon failing to respond to treatment, a bone marrow biopsy confirmed the diagnosis of BMN. Unfortunately, the patient passed away.

There is very limited data in the literature on the epidemiology of APS in Egypt. Even when present, they typically feature small cohorts that lack diverse characteristics, making it difficult to conclude. In a study by Morad et al, one of the few studies in the literature on APS in an Egyptian cohort, 91.7% of patients were females, and 80% of patients had secondary APS [14]. Another study by Abd El-Moniem et al showed similar characteristics with 91.2% females and 71.6% secondary APS [15]. Thus, the incidence of primary APS in male patients in Egypt remains poorly studied, further emphasizing the significance of this case study. This case report highlights the urgent need for further research and country-specific data to address this knowledge gap, thereby enhancing future management. Adding to the rarity of this presentation, BMN in Egyptian patients has been rarely reported. After a thorough review of the literature, only one study has explored BMN in Egypt [16]. Elgamal et al examined 5,043 bone marrow biopsies of cancer patients at the National Cancer Institute to assess the prevalence of BMN [16]. Fifteen of the 5,043 biopsies featured BMN, resulting in a prevalence of 0.3% [16]. They reported an association between BMN and poor prognosis, with none of the patients surviving beyond 6 months from the time of BMN diagnosis [16]. No other studies have examined BMN in Egypt. Thus, this presents the first case report of BMN in Egypt in the literature. It is also the first study examining BMN due to a benign etiology in Egypt.

In 1995, Bulvik et al published the first case report of BMN in a patient with APS [12]. The patient responded to treatment with methylprednisolone [12]. Interestingly, although SLE had been previously excluded, this patient later developed positive ANA and anti-Smith antibodies [12]. Despite not meeting the diagnostic criteria for SLE, the patient was considered to be “lupus-like” [12]. The authors inferred that the high antibody titers in this patient may have had a role in the pathogenesis of BMN [12]. In 1997, a second case report was published by Paydas et al on a 27-year-old female [13]. The patient had pancytopenia refractory to treatment with steroids and plasma exchange [13]. Despite testing negative for ANA and anti-dsDNA antibodies, investigations were positive for anti-SM antibodies [13].

Table 4: Literature comparison table of cases of BMN in APS

Study ID	Gender/Age	Geographic location	APS type	Antibody levels	Treatment	Outcome
Badra 2025 (this case)	M/32	Egypt	Triple-positive APS ANA & anti-dsDNA negative.	Moderate positive titers Anti-cardiolipin IgG: 39.8 U/ml Anti-cardiolipin IgM: 1.7 U/ml	Hydroxychloroquine, prednisolone, & cyclophosphamide. Then rituximab & dexamethasone.	No response to treatment. Death due to septic shock.
Paydas 1997 [13]	F/27	Turkey	Not specified ANA & anti-dsDNA antibodies negative, but anti-SM antibody positive.	Anti-cardiolipin IgG: 215 U/I Anti-cardiolipin IgM: 48 U/I	Steroids, transfusion, & plasma exchange.	Pancytopenia did not respond. The patient discharged herself.
Bulvik 1995 [12]	F/23	South Africa	Not specified Later became ANA & anti-Smith antibodies positive.	High antibody titers	Methylprednisolone	The patient responded to treatment.

BMN, bone marrow necrosis; APS, antiphospholipid syndrome

(Table 4) compares the three cases of BMN in APS, providing insight into demographics, management, and outcomes. Although our case is similar, it features a male patient. The patient's history of bilateral DVTs, pulmonary embolism, and myocardial infarction provided valuable insight into the severity of the patient's manifestations. The antibody titers in our patient were not as high as those reported in the two previous case reports **(Table 3)** and **(Table 4)**, suggesting that the pathogenesis of BMN in patients with APS may not be solely explained by high antibody titers. Unfortunately, our patient did not respond to treatment and passed away shortly after being diagnosed with BMN. This is in line with the poor prognosis that has been reported with BMN due to other etiologies [16, 8].

BMN may be suspected in patients with bone pain, fever, cytopenias, and elevated LDH – all of which are non-specific findings, presenting a diagnostic challenge [17]. Thus, clinical findings alone are insufficient and warrant further investigations [17]. Our patient had fever, anemia, thrombocytopenia, and elevated LDH, consistent with BMN. Bone marrow biopsy can confirm the presence of BMN [17]. It shows necrotic areas with disrupted bone marrow architecture, eosinophilic debris, and ghost cells [17]. These features were seen in our patient. Upon diagnosing BMN, thorough history-taking, clinical examination, and investigations are necessary to identify the underlying cause, if it was not already known [17]. In patients with BMN, the treatment is aimed at the underlying primary disorder. Despite treatment attempts, it carries an extremely poor prognosis and is rapidly fatal in most cases, consistent with what was seen in this case as well [18].

This case report of BMN in a male patient with APS is of significance due to the rarity of this association. However, it is not possible to establish a cause-and-effect relationship or draw conclusive findings from a single case report. Another potential limitation is the temporal association between cyclophosphamide and BMN, suggesting the possibility of cyclophosphamide-induced bone marrow toxicity. Alternative causes for bone marrow necrosis in this patient include drugs, infections, and other autoimmune diseases [17]. The poorly understood pathogenesis of both BMN and APS further hinders our ability to fully comprehend the presented case. More case reports from clinicians who come across BMN in patients with APS can help broaden our understanding of the pathogenesis, presentation, management, and outcomes. Each case report will provide a unique perspective that, together, contributes to our overall understanding of this rare complication.

4. Conclusions

BMN is an extremely rare complication of APS. We present the third reported case of BMN in a patient with APS. Unfortunately, the patient did not respond to treatment attempts and passed away two months after the BMN diagnosis. More case reports are needed to better understand this association.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Informed consent

We obtained written informed consent for publication from the patient.

Large Language Model

None

Authors Contribution

MAH, MB contributed to the original draft writing. DAN supervised the project. MS administered the project. Reviewing and editing were performed by MAH, MB, MS, and NS. All authors read and approved the final content.

Data Availability

The data supporting the findings of this case report are included within the article and its supplementary materials. Additional de-identified information may be made available upon reasonable request from the corresponding author.

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ASIDE Case Reports

Case Report

Portal Venous Gas Following Laparoscopic Rectal Surgery: A Case Report of Internal Herniation without Bowel Necrosis

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ABSTRACT

The presence of free air (pneumatosis) in the main and intrahepatic portal veins generally indicates acute mesenteric ischaemia, often accompanied by bowel necrosis. Internal herniation (IH) is a rare but serious complication of laparoscopic rectal surgery, where the mesenteric window is deliberately left open. IH, followed by mechanical intestinal obstruction, can cause intestinal damage, ischaemia, and necrosis, which may manifest as hepatic portal venous gas (HPVG) on imaging. In cases linked to IH, mesenteric ischaemia often results in a severe and potentially fatal clinical course. Here, despite computerised tomography findings suggestive of advanced ischaemia, a young patient underwent successful surgical intervention for IH. Rapid diagnosis and prompt emergency surgery enabled the reduction of the herniation without bowel resection, preventing progression to irreversible complications. Although leaving mesenteric windows open maintains anastomotic perfusion, this practice may carry a risk of IH in selected patients. Importantly, no bowel resection was needed, illustrating the importance of early detection. Further comprehensive studies are recommended to explore this issue.

1. Introduction

The presence of gas in the portal vein and/or its intrahepatic branches is most commonly associated with enteric bacterial translocation due to mesenteric ischemia or intestinal necrosis. However, other causes of HPVG include peritonitis, postoperative changes following abdominal surgery, intestinal necrosis, and gastrointestinal bleeding [1, 2]. This condition is generally expected more in elderly patients presenting with an acute abdomen and as a result of thromboembolic events [3]. Fatal clinical course is more frequently observed in cases involving severe intestinal damage, delayed intervention, advanced age, complete obstruction due to intestinal pathologies, and comorbid cardiovascular diseases [1, 3, 2, 4]. Similar results are expected in complete obstructions caused by IH and associated intestinal necrosis [5].

IH is a clinical condition characterised by the abnormal displacement of the small bowel through a mesenteric defect of varying aetiology, potentially leading to complete or near-complete intestinal obstruction. [6]. IH may arise congenitally, develop secondary to prior surgery, or result from intentionally preserved mesenteric openings during laparoscopic rectal surgery [5, 7, 6]. In cases of partial obstruction, patients may present with mild abdominal pain and vomiting, whereas complete obstruction is associated with a more severe clinical course [8]. The progression of obstruction, intestinal oedema, mucosal damage, and subsequent bacterial translocation can lead to pneumatosis intestinalis and gas entry into the portal circulation [9]. Although IH is a rare cause of acute abdomen, delayed diagnosis and intervention can result in ischemia, progression to necrosis, and necessitate extensive small bowel resection [5, 6]. This case report highlights a rapidly progressing, complex acute abdomen with massive HPVG on imaging in a patient who had recently undergone laparoscopic low anterior resection (LLAR), emphasising the critical need for prompt surgical intervention.

2. Case Presentation

A 35-year-old male patient with no history of smoking, alcohol use, or comorbidities presented to our emergency department with a two-day history of abdominal pain, nausea, and vomiting. He had undergone a laparoscopic low anterior resection (LLAR) with a loop ileostomy nine months earlier for a high-grade dysplastic (HGD) tubulovillous adenoma of the rectum. The loop ileostomy was reversed three months after the primary surgery. Following the ileostomy closure, the patient experienced intermittent abdominal pain but had no admission for emergency care until the current presentation.

On physical examination, the patient exhibited generalised abdominal tenderness and guarding across all quadrants. Vital signs revealed a blood pressure of 104/62 mmHg, a pulse rate of 98 beats per minute, and a body temperature of 36.4°C.

Laboratory tests revealed a white blood cell (WBC) count of $14.8\times10^3/mm^3$, haemoglobin level of 12 g/dL, and a platelet count of $382\times10^3/mm^3$. The C-reactive protein (CRP) level was 3.31 mg/L, with neutrophils comprising 75.5% of the leukocyte differential.

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Table 1: Laboratory Parameters and Clinical Interpretation

Parameter	Value	Reference Range	Units	Interpretation
White blood cell count	14.8	3.5–10.5	$\times 10^3/mm^3$	Elevated
Hemoglobin	12.0	13.5–17.5	g/dL	Decreased
Platelet count	382	150–450	$\times 10^3/mm^3$	Normal
C-reactive protein	3.31	<5.0	mg/L	Normal
Neutrophils	75.5	50.5–74.7	%	Elevated
Amylase	75	28–100	U/L	Normal
Arterial pH	7.38	7.35–7.45	—	Normal
Arterial lactate	6.4	1.0–1.5	mmol/L	Elevated

Reference ranges are based on institutional laboratory standards. Values outside the reference range are indicated as elevated or decreased.
CRP, C-reactive protein; g/dL, grams per deciliter; mg/L, milligrams per liter; mm^3, cubic millimeters; mmol/L, millimoles per liter; U/L, units per liter.

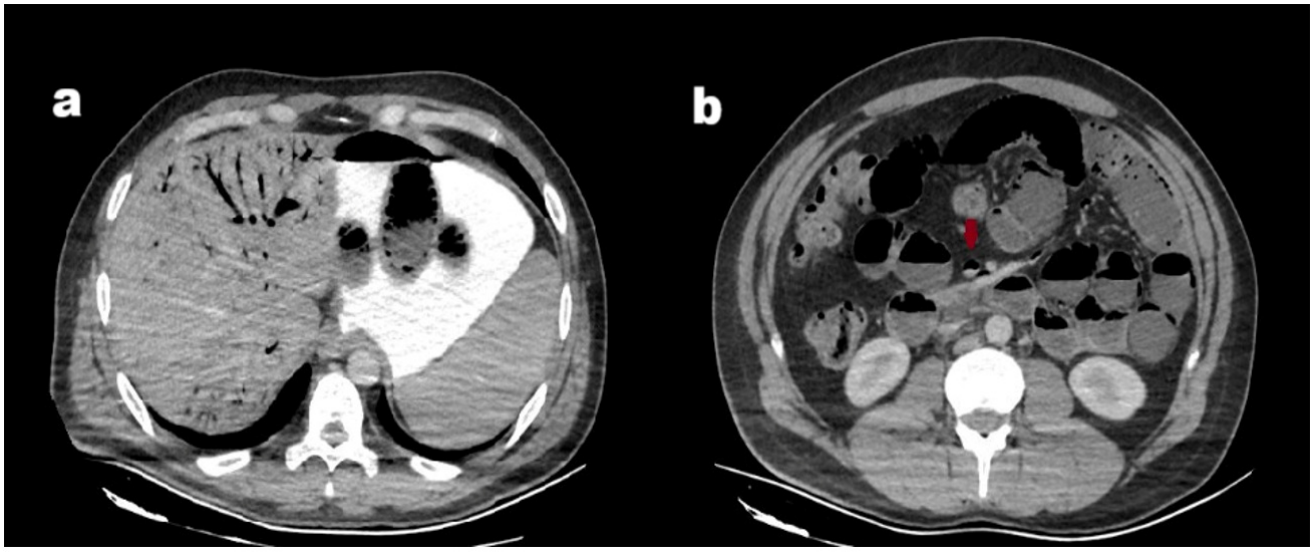

Figure 1: Multiple air foci in the main portal vein and its branches with shadows in the superior mesenteric vein (SMV). (a) Multiple air foci within the intrahepatic portal venous branches. (b) Air shadows observed in the superior mesenteric vein (arrow), air-fluid levels in the small intestine, and pneumatosis in the wall of the small intestine.

Serum amylase was 75 U/L. Arterial blood gas analysis showed a pH of 7.38 and an elevated lactate level of 6.4 mmol/L **(Table 1)**.

Contrast-enhanced abdominal and pelvic computed tomography (CT) with oral and intravenous contrast demonstrated dilated ileal and jejunal loops with luminal air-fluid levels and intramural gas. Air was also noted within the superior mesenteric vein, portal vein branches, and multiple intrahepatic portal venous branches **(Figure 1)**. These findings were consistent with HPVG secondary to bowel ischemia, likely resulting from mesenteric obstruction, IH, or other delayed postoperative complications. Given the imaging findings and clinical status, urgent surgical intervention was indicated. The patient was taken to the operating room within 5–6 hours of presentation to the emergency department.

Upon open laparotomy, a moderate amount of serous fluid was found in the peritoneal cavity. Scattered areas of mild ischemia were observed along the small bowel loops. A mesenteric defect adjacent to the left colon had permitted complete herniation of the entire small intestine into the right hemi-abdomen, resulting in medial displacement of the left colon **(Figure 2)**.

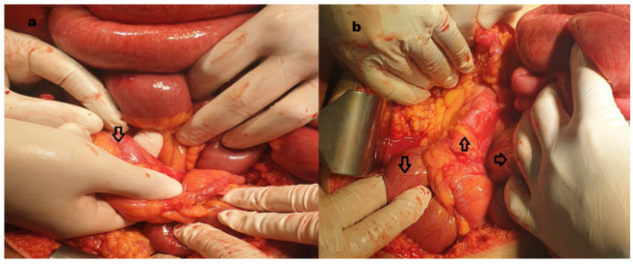

Figure 2: Mesenteric defect in the left colon and herniated small bowel. (a) Mesenteric defect in the left colon (arrow↓), with the surgeon's fingers passing through the defect in the left mesentery. (b) Mesenteric defect in the left colon showing terminal ileum (arrow↓), left colon (arrow↑), and herniated mesentery (arrow→).

The herniated small bowel loops were manually reduced, and serosal injuries (without full-thickness compromise) were repaired primarily. Peristalsis was preserved in the ischemic segments, and the return of normal serosal colour following warm compress

application indicated tissue viability. Due to the large size of the mesenteric defect and medial displacement of the left colon, the colon was secured to the lateral parietal peritoneum using interrupted sutures. The mesenteric defect was then closed in a tension-free manner at the medial retroperitoneal region to prevent stricture formation. After suturing, the viability of the colon was reassessed and confirmed. The patient was subsequently transferred to the intensive care unit for postoperative monitoring. Following consultation with the Infectious Diseases team, empiric antibiotic therapy with meropenem and vancomycin was initiated immediately after surgery. The antibiotic administration was continued over seven days, with blood cultures remaining negative throughout.

Subsequent postoperative monitoring showed a steady decline in leukocyte count and acute-phase reactants, with no significant abnormalities in vital signs. A gradual oral diet was initiated on postoperative day (POD) 3, and the patient was transferred to the surgical ward on POD 4. He was discharged on POD 7 with a normal diet and stable clinical status. At the 1-week follow-up visit, no complications were observed, and sutures were removed. No signs of recurrence or late complications were noted during the 6-month follow-up period.

3. Discussion

HPVG develops when gas produced in the intestinal wall due to pneumatosis—secondary to bacterial translocation—enters the portal circulation and subsequently migrates into the hepatic venous system [1]. This condition is associated with a high mortality rate and is typically detected on CT imaging, most often indicating irreversible intestinal ischemia and necrosis [1, 3, 2, 4]. Although rare in young patients, congenital anomalies such as Ladd's bands, as well as postoperative complications leading to bowel obstruction or injury, should be thoroughly investigated as potential secondary aetiologies [5, 7, 6]. IH is a serious condition that can cause complete bowel obstruction and present as an acute abdomen. It may occur congenitally or develop postoperatively, especially following colorectal surgery [9, 8, 7]. In patients undergoing left colon or rectal surgery, the inferior mesenteric artery (IMA) is typically ligated, and the bowel mesentery is intentionally left open to preserve perfusion to the anastomotic site [7, 10]. Leaving the mesentery open may increase the risk of IH. Postoperative IH related to mesenteric defects can manifest early or several months after surgery, with the highest incidence reported around the fourth postoperative month. IH occurs in 2–3.6% of patients within three years following laparoscopic colorectal resection. Although the overall incidence after laparoscopic colorectal surgery is low (approximately 0.65%), IH carries a mortality rate of 20–50% when complicated by bowel ischemia, underscoring the critical need for early diagnosis and intervention [7, 11, 10].

CT is the most commonly used imaging modality for diagnosing IH; however, it may not always provide definitive confirmation. Therefore, IH should be considered in the differential diagnosis of patients presenting with unexplained abdominal pain, subileus or ileus episodes, or recurrent vomiting. Definitive diagnosis and identification of the underlying cause are typically established during surgical exploration [11].

This case is notable for several reasons: the patient's young age, the early postoperative onset of herniation, complete displacement and transposition of the small bowel, and the presence of massive HPVG despite the absence of bowel necrosis. Unlike most cases reported in the literature where HPVG predicts irreversible necrosis, this patient achieved full recovery following successful reduction without bowel resection, culminating in complete remission. These findings underscore the critical importance of managing mesenteric defects after laparoscopic rectal surgery. However, the data remains divided on whether mesenteric defects should be routinely closed during the initial operation [12, 13]. Routine closure of mesenteric defects is often avoided due to concerns about compromising anastomotic perfusion, technical complexity, and increased operative time [12]. However, some studies suggest that large mesenteric defects significantly increase the risk of IH, and that closure may help prevent this complication [10, 13]. In cases where rapid weight loss or minimal postoperative adhesion formation is anticipated, careful intraoperative assessment of mesenteric defects and selective closure in high-risk patients should be considered.

4. Conclusions

HPVG may indicate an acute intra-abdominal event such as IH or mesenteric ischemia, particularly in elderly patients or those with a history of abdominal surgery. IH following laparoscopic colorectal surgery is a rare but serious complication that can result in HPVG. Early diagnosis and prompt surgical intervention are critical for survival in such cases. While there is no established consensus on routine closure of mesenteric defects, in our case, lateral fixation of the colon may have played a role in preventing recurrent herniation. Emergency surgical exploration remains lifesaving in suspected cases, as any delay may lead to intestinal necrosis, perforation, sepsis, or the need for extensive bowel resection (all associated with high morbidity and mortality). As a single case report, the findings are limited in generalizability. Further multicenter studies are necessary to better evaluate the risks and benefits of routine mesenteric defect closure in laparoscopic colorectal surgery.

Conflicts of Interest

The authors declare that they have no competing interests.

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All necessary consent documents to publish images and clinical information relating to the cases were obtained from the patient, written in Turkish. Only accepted images were shared.

Large Language Model

The authors declare that artificial intelligence and AI-assisted technologies were not used in the article.

Authors Contribution

AT contributed to review, translation, and editing; EK was responsible for writing; UD contributed to review and editing; UK managed reference control; and DT contributed to conceptualisation (supporting).

Data Availability

Data supporting the findings of this study are available within the paper. The video of the case is available from the corresponding author upon request.

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ASIDE Case Reports

Case Report

Outcome of Kidney Transplant Patients Following Treatment with Checkpoint Inhibitors: A Case Series

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ABSTRACT

Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment by enhancing immune surveillance against tumors. However, their use in kidney transplant recipients presents a significant challenge due to the risk of immune-mediated graft rejection. This retrospective case series highlights four kidney transplant recipients treated with ICIs for various malignancies, revealing the complex interplay between oncologic outcomes and transplant function. Two of four patients developed severe acute kidney injury (AKI), leading to dialysis-dependent graft loss despite high-dose corticosteroid therapy. One patient exhibited partial renal recovery following transient dialysis. In contrast, another patient maintained stable graft function despite prolonged ICI therapy. Oncologic outcomes varied, with two patients achieving significant tumor regression, while others experienced disease progression. These cases underscore the need for careful immunosuppressive management and close monitoring when administering ICIs in transplant recipients. The findings emphasize the importance of individualized treatment strategies to optimize both cancer control and graft survival.

1. Introduction

Introduction Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment by enhancing the immune system's ability to recognize and destroy tumor cells. Agents such as pembrolizumab, cemiplimab, atezolizumab, and durvalumab work by blocking the programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) pathways, restoring T-cell activity, and overcoming tumor immune evasion. These agents have been particularly effective in treating cancers such as advanced melanoma, non-small cell lung cancer, and cutaneous squamous cell carcinoma (SCC) [1, 2].

However, the use of ICIs in solid organ transplant recipients, particularly kidney transplant recipients, presents a major challenge. These individuals rely on lifelong immunosuppression to prevent graft rejection, which inherently increases their risk of malignancies. The introduction of ICIs can precipitate immune activation and acute allograft rejection, often within weeks of initiation, resulting in graft dysfunction, dialysis dependence, or graft loss [3, 4, 5]. Balancing oncologic control with preservation of the transplanted organ is complex, as immunosuppressive minimization may improve anti-tumor responses but exacerbate rejection risk. Prior studies have reported rates of T-cell-mediated rejection and vascular inflammation following ICI therapy, along with high rates of cancer progression and mortality in this population [3, 5].

This case series aims to explore the outcomes of kidney transplant recipients who were treated with ICIs for various malignancies, providing insights into both the oncologic and renal responses to this emerging class of drugs. By examining the experiences of four patients who underwent ICI therapy, this series highlights the complexities of managing cancer and transplant function simultaneously. The varying responses to ICI therapy underscore the need for individualized treatment strategies, particularly in this vulnerable population. Additionally, the case series illustrates the challenges in optimizing immunosuppressive regimens to mitigate the risk of graft rejection while maximizing the efficacy of cancer therapy. The ongoing challenge of improving both oncologic outcomes and graft survival in transplant recipients requires further research and a multidisciplinary approach to patient care [1, 3]. Our study highlights the urgent need for individualized immunosuppressive strategies and close multidisciplinary coordination to optimize both graft preservation and cancer outcomes in this high-risk population.

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2. Case Presentation

2.1. Case 1

A 71-year-old Caucasian male with a history of chronic kidney disease (CKD) secondary to IgA nephropathy underwent a preemptive living donor kidney transplant. The patient received induction therapy with intravenous basiliximab and maintenance immunosuppression consisting of extended-release tacrolimus, mycophenolate mofetil (MMF), and Prednisone. His baseline serum creatinine ranged between 1.3 and 1.5 mg/dL. The post-transplant course was complicated by neutropenia four months after transplantation, necessitating treatment with filgrastim. Given persistent neutropenia, MMF was replaced with everolimus. However, his condition worsened, and he developed low-grade cytomegalovirus (CMV) viremia. Consequently, everolimus was discontinued, and he was maintained on a dual immunosuppressive regimen of tacrolimus and prednisone. Approximately 21 months post-transplant, the patient was diagnosed with poorly differentiated squamous cell carcinoma of the scalp. Initial treatment involved Mohs surgery, followed by local wide excision and salvage surgery with forehead flap reconstruction nine months later. Due to the aggressive nature of his malignancy, cemiplimab therapy was recommended. In preparation for this, tacrolimus was replaced with sirolimus, maintaining target trough levels of 3–5 ng/mL. The patient received the first dose of cemiplimab one week later.

Fifteen days following cemiplimab administration, he presented with severe AKI and nephrotic-range proteinuria. His serum creatinine rose to 10.2 mg/dL (reference range: 0.59–1.04 mg/dL), and urine protein excretion reached 26 g/g (reference range: <150 mg/day). A kidney biopsy revealed widespread cortical coagulative necrosis, moderate tubulitis, and focal severe intimal arteritis. He was treated with an intravenous pulse methylprednisolone, followed by a gradual oral Prednisone taper. Despite aggressive immunosuppression, the patient's renal function failed to recover, resulting in dialysis dependence. One month later, the patient received a second dose of cemiplimab. Following this infusion, he developed gross hematuria, which responded to intravenous pulse methylprednisolone. Given the resolution of hematuria, transplant nephrectomy was deferred. However, oncology specialists advised that nephrectomy should be reconsidered if further cemiplimab therapy was required. To date, the patient has demonstrated significant improvement in his cutaneous malignancy. This case illustrates a severe ICI-associated rejection resulting in graft loss despite pre-emptive adjustment to mammalian target of rapamycin (mTOR) inhibitor-based immunosuppression.

2.2. Case 2

A 66-year-old Caucasian male with end-stage kidney disease secondary to diabetes mellitus and hypertension underwent a deceased donor kidney transplant following 19 months of dialysis. He received induction therapy with anti-thymocyte globulin and was maintained on a triple immunosuppressive regimen of immediate-release tacrolimus, MMF, and Prednisone. His baseline serum creatinine stabilized between 0.8 and 1.0 mg/dL. Approximately two years post-transplant, he was diagnosed with invasive squamous cell carcinoma of the oropharynx and underwent tonsillectomy followed by radiation therapy. However, 18 months later, he experienced cancer recurrence, with biopsy-confirmed invasive SCC of the vallecula and high-grade squamous intraepithelial lesions, along with metastatic spread to the lungs. In response, MMF was discontinued, and three months later, tacrolimus was also withdrawn. The patient subsequently underwent left oropharyngectomy and total laryngectomy, followed by multiple chemotherapy cycles with cisplatin, carboplatin, docetaxel, and cetuximab. Additionally, he received palliative radiation therapy for his lung metastases. Given the progression of his disease, pembrolizumab therapy was initiated. In preparation, he was transitioned to sirolimus. Within 19 days of receiving his second dose of pembrolizumab, he developed oliguric AKI, with serum creatinine rising from a baseline of 0.8 mg/dL to 4.5 mg/dL (reference range: 0.59–1.04 mg/dL). High-dose corticosteroids (500 mg IV methyl prednisone x 3) failed to reverse the AKI, and dialysis was initiated. However, renal recovery was achieved after one month. His current serum creatinine ranges between 1.4 and 1.7 mg/dL. Despite pembrolizumab therapy, his malignancy continued to progress. He is currently being treated with capecitabine for disease control. This case highlights the potential for partial renal recovery following ICI-associated AKI and the limitations of ICI efficacy in aggressive metastatic SCC.

2.3. Case 3

A 65-year-old Caucasian male with end-stage kidney disease secondary to polycystic kidney disease received a prior kidney transplant at the age of 54. Over time, he developed chronic allograft nephropathy, necessitating a second preemptive living donor kidney transplant nine years later. Perioperatively, he was induced with anti-thymocyte globulin and maintained on immediate-release tacrolimus, MMF, and prednisone. His baseline serum creatinine remained stable at 0.9–1.1 mg/dL (reference range: 0.59–1.04 mg/dL). Six months post-transplant, the patient was diagnosed with SCC of the face and underwent multiple surgical excisions, including Mohs surgery. Given the persistent recurrence of skin cancer lesions, MMF was discontinued seven months after the initial SCC diagnosis. Ten months later, everolimus was introduced while maintaining a reduced dose of Tacrolimus. Despite these modifications, the patient continued to experience recurrent SCC lesions. Approximately two years later, cemiplimab was initiated. However, after one year of ICI therapy, he developed poorly differentiated SCC with lymph node involvement and metastasis to the left parotid gland. He subsequently underwent surgical excision of the metastatic lesions, including removal of the left parotid gland, followed by radiation therapy. In response, tacrolimus was discontinued, and the patient was maintained on dual immunosuppression with everolimus and prednisone. Notably, he has experienced no evidence of immune-mediated rejection despite long-term ICI exposure. He continues to receive cemiplimab infusions every three weeks under close monitoring. This case demonstrates that sustained graft function may be possible with mTOR inhibitor-based regimens and close monitoring during prolonged ICI therapy.

2.4. Case 4

A 69-year-old Caucasian male with primary biliary cirrhosis underwent an orthotopic liver transplant. AKI, necessitating dialysis, complicated his postoperative course. Given persistent kidney dysfunction, he subsequently received a deceased donor kidney transplant under the safety net pathway approximately six months later. For induction, he received anti-thymocyte globulin, followed by maintenance immunosuppression with immediate-release tacrolimus, MMF, and prednisone. His baseline serum creatinine stabilized between 0.8 and 1.0 mg/dL (reference range: 0.59–1.04 mg/dL). However, within two months of kidney transplantation, he experienced recurrent urinary tract infections, septic shock, fungemia, AKI, and BK viremia. Due to the high infectious burden, MMF was discontinued. The patient required dialysis for two weeks but eventually regained renal function, with serum creatinine stabilizing at 2.5–3.0 mg/dL. One year post-kidney transplant, he was diagnosed with invasive SCC with lymph node involvement and pulmonary metastases. Despite multiple surgical

Table 1: Clinical Characteristics and Outcomes of Kidney Transplant Recipients Treated with Immune Checkpoint Inhibitors: Case Series

Parameters	Patient 1	Patient 2	Patient 3	Patient 4
Birth year	1953	1958	1954	1948
Sex	male	male	male	male
Race	Caucasian	Caucasian	Caucasian	Caucasian
Etiology of kidney disease	IgA nephropathy	DM, HTN	PCKD	CNI nephrotoxicity
Months on dialysis	0	19	0	HD for AKI post-OLT (8 days)
Date of transplant	8/11/2021	12/7/2019	9/16/2019	5/10/2018
Donor age	56	29	54	37
Donor sex	female	male	male	male
Donor type	LUKT	DDKT, DCD, PHS high risk	LUKT	DDKT, DCD, PHS high risk
Induction	Basiliximab	ATG	ATG	ATG
Maintenance immunosuppression	Tacrolimus XR (Envarsus), MMF, Prednisone	Tacrolimus IR (Prograf), MMF, Prednisone	Tacrolimus IR (Prograf), MMF, Prednisone	Tacrolimus IR (Prograf), MMF, Prednisone
Nadir serum creatinine	1.3-1.5 mg/dl	0.8-1 mg/dl	0.9-1.1 mg/dl	0.8-1 mg/dl
Major events post-transplant	Leukopenia, requiring Filgrastim 12/2021-1/2022 MMF switched to Everolimus in 4/2022, but neutropenia worsened Low-grade CMV viremia 4/2022: kept on Tacrolimus, Prednisone only	Tonsillectomy (8/2021)	n/a	OLT (12/12/2017) Multiple episodes of early post-transplant UTI, sepsis, septic shock, fungemia, AKI (required RRT 7/2-17/2018) BK viremia (7/2018-4/2019) BK viruria (6/2018-1/2020)
Cancer diagnosis	Aggressive squamous cell skin CA on the head	Invasive squamous cell CA of the oropharynx with lung metastasis	Poorly differentiated squamous cell skin CA with lymph node involvement and metastasis to the parotid gland	Invasive squamous cell skin CA with lymph node involvement and metastasis to the lungs
Pathology	Acantholytic invasive squamous cell CA, poorly differentiated (5/2023), Dermal deposit of poorly differentiated CA (1/2024)	Tonsillar squamous cell CA (8/2021) Invasive squamous cell CA of the vallecula with background of high-grade squamous intraepithelial lesion (severe dysplasia) (2/2023)	Poorly differentiated squamous cell skin CA	Invasive squamous cell skin CA, poorly differentiated, acantholytic with lymphovascular invasion
Date of diagnosis	5/20/2023	8/2/2021	3/16/2020	6/26/2019
Treatment received for cancer	Mohs surgery Efudex Local wide excision, salvage surgery, local forehead flap reconstruction (2/2024)	Tonsillectomy, surgical excision, radiation therapy (8/2021) L oropharyngectomy, total laryngectomy (5/2023), Cisplatin, Docetaxel, Cetuximab x 1 cycle (7/2023), Cetuximab monotherapy x 2 cycles (7/2023), Carboplatin, Docetaxel, Cetuximab x 3 cycle (11/2023), Palliative radiation of lung nodule (11/2023), Carboplatin, Docetaxel x 4 cycles (1-3/2024) Pembrolizumab monotherapy x 2 cycles (5/2024) Disease progression noted, so switched to Capecitabine (9/2024 onwards)	Multiple surgical excision of skin CA, Mohs surgery; Surgical resection of L parotid gland (9/2024), followed by radiation therapy	Multiple surgical excisions; Mohs surgery; radiation therapy

Table 1 (continued): Clinical Characteristics and Outcomes of Kidney Transplant Recipients Treated with Immune Checkpoint Inhibitors: Case Series

Parameters	Patient 1	Patient 2	Patient 3	Patient 4
Immunosuppression changes with malignancy	Switched Tacrolimus to Sirolimus (level 4-5 ng/ml) late 3/2024	MMF discontinued 4/2023 due to CA recurrence FK discontinued 8/2023 Switched to Sirolimus (5/2024) then Everolimus (11/2024)	MMF discontinued (10/2020); Everolimus added to low-dose Tacrolimus (8/2021); Tacrolimus discontinued (9/2024) due to evidence of spread to lymph node and parotid gland	MMF discontinued (3/2018) due to multiple infections and BK viremia
EGFR before Cemiplimab	59 ml/min/1.73 sq.m	105 ml/min/1.73 sq.m	>60 ml/min/1.73 sq.m	25 ml/min/1.73 sq.m
Date of the checkpoint inhibitor	Cemiplimab started on 4/11/2024	Pembrolizumab started on 5/1/2024	Cemiplimab began on 9/21/2023 and given q3weeks	Cemiplimab started on 9/12/2019 and given q3weeks
EGFR after Cemiplimab	21 ml/min/1.73 sq.m	29 ml/min/1.73 sq.m	59 ml/min/1.73 sq.m	25 ml/min/1.73 sq.m
Date of rejection	4/30/2024	5/2024	n/a	n/a
Presentation of AKI	Peak serum crea 10.2 mg/dl Proteinuria 26 g/g			
Kidney transplant biopsy	Widespread coagulative necrosis of the cortex, moderate tubulitis, focal severe intimal arteritis Banff g0, i1, t2, v2, cg0, ci1, ct2, cv3, ah1.5, ptc2, c4d1, mm0, ti2	Not done; presumed rejection	n/a	n/a
DSA	Neg 4/2024	Neg 6/2024	Neg 10/2024	
Treatment received for rejection	Methylprednisolone IV pulse + Prednisone taper	Methylprednisolone IV pulse x 2 cycles	n/a	n/a
Graft outcome	Return to hemodialysis on 4/28/2024	Required HD 6/21-27/2024, then recovered renal function	Excellent graft function	Functioning graft with CKD stage 4

ICI, Immune Checkpoint Inhibitor; AKI, Acute Kidney Injury; DM, Diabetes Mellitus; HTN, Hypertension; PCKD, Polycystic Kidney Disease; CNI, Calcineurin Inhibitor; HD, Hemodialysis; OLT, Orthotopic Liver Transplant; LUKT, Living Unrelated Kidney Transplant; DDKT, Deceased Donor Kidney Transplant; DCD, Donation After Circulatory Death; PHS, Public Health Service; ATG, Anti-Thymocyte Globulin; MMF, Mycophenolate Mofetil; XR, Extended Release; IR, Immediate Release; CMV, Cytomegalovirus; CA, Carcinoma; SCC, Squamous Cell Carcinoma; UTI, Urinary Tract Infection; RRT, Renal Replacement Therapy; EGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease; DSA, Donor-Specific Antibody; BK, BK Virus.

excisions, Mohs surgery, and radiation therapy, his cancer remained progressive. The patient transitioned to palliative care. Approximately one year after his cancer diagnosis, his dermatologist recommended cemiplimab. Following the initiation of cemiplimab, he achieved significant oncologic remission, allowing him to discontinue palliative care. Despite baseline CKD and prior infectious complications, the patient has remained dialysis-free with stable graft function following ICI therapy. This case suggests that ICIs may be cautiously used in patients with impaired graft function and limited therapeutic options, especially when cancer prognosis improves.

3. Discussion

ICIs, including PD-1 inhibitors such as pembrolizumab and cemiplimab, as well as PD-L1 inhibitors like atezolizumab and durvalumab, have significantly advanced cancer treatment by enhancing the immune response against cancer cells [2]. Agents like these inhibit the interactions between PD-1 receptors on immune cells and PD-L1 on neoplastic cells, thereby preventing the tumor's ability to evade the immune system. This enables the immune system to identify and target cancer cells with greater efficacy [6]. However, their use in kidney transplant recipients presents unique challenges due to the risk of immune-mediated graft dysfunction, often manifesting as acute rejection. This case series highlights four kidney transplant recipients who developed different types of malignancies requiring ICI therapy, with varying outcomes in renal function and oncologic response.

3.1. Graft Rejection and Kidney Function Deterioration

The activation of the immune system by ICIs has been observed to provoke acute rejection in transplant recipients, a critical consideration illustrated by the experiences of patients 1 and 2. Patient 1, who was treated with cemiplimab for advanced, poorly differentiated SCC on his scalp, a therapy approved by the FDA in 2018 [7], suffered severe AKI. This was characterized by significant proteinuria and a biopsy showing extensive coagulative necrosis, tubulitis, and intimal arteritis. Despite intensive treatment with high-dose steroids, the patient's condition progressed to the point where dialysis became necessary. Similarly, patient 2 began experiencing oliguric AKI shortly after starting pembrolizumab for recurrent oropharyngeal cancer. Although this patient initially required dialysis, there was a subsequent partial recovery of renal function.

These clinical scenarios are supported by a systematic review and meta-analysis conducted by Wang et al., which underscore the common complications of T-cell-mediated rejection and microvascular inflammation in solid organ transplant recipients undergoing ICI therapy. The review, encompassing over 19,000 patients across 112 trials, noted graft failure rates ranging from 40% to 50%. Furthermore, it highlighted that those fatal toxic effects, though relatively rare, occurred in 0.3% to 1.3% of the patients. The most lethal complications were myocarditis, pneumonitis, hepatitis, and various neurological events, emphasizing the need for vigilant monitoring and prompt intervention [4, 5].

Conversely, patients 3 and 4, who received cemiplimab for advanced CSCC of the head and neck, exhibited stable renal function. Despite ongoing ICI therapy, patient 3 showed no significant renal impairment. Patient 4 maintained graft viability, albeit with suboptimal kidney function exacerbated by previous medical complications such as sepsis and BK viremia. These cases suggest that modulation of immunosuppression, particularly through the use of mTOR inhibitors such as everolimus and sirolimus, may help reduce rejection risks while preserving anti-tumor immunity. Notable in this context is the potential dual benefit of mTOR inhibitors in managing virus-associated post-transplant malignancies and certain cancers like Kaposi sarcoma and mantle cell lymphoma, as highlighted by Fijter et al [8]. Although these inhibitors are primarily cytostatic—halting tumor growth rather than causing regression—recent studies suggest that their use in early conversion to an mTOR inhibitor-based regimen may diminish the cumulative burden of non-melanoma skin cancers.

Despite these promising indications, the evidence remains insufficient to advocate the primary use of mTOR inhibitors as a universal strategy against all malignancies in transplant recipients. The contrasting outcomes between patients underscore the complexity of using ICIs in this vulnerable population and the crucial role of tailored therapeutic strategies based on individual risk assessments and treatment responses [8].

3.2. Oncologic Outcomes and ICIs Efficacy

ICIs have demonstrated variable effectiveness in treating SCC in our cohort. Patient 1 experienced remarkable regression of aggressive, poorly differentiated cutaneous SCC with cemiplimab treatment, although resulting in the loss of graft function. Conversely, patient 2 failed to achieve cancer control with pembrolizumab and subsequently switched to oral capecitabine as a second-line palliative treatment due to disease progression. Patient 3, after one year of Cemiplimab treatment, experienced recurrence and metastasis of poorly differentiated SCC to the left parotid gland, requiring additional salvage radiation and surgical procedures. Patient 4, initially receiving treatment with palliative intent, experienced a remarkable response to cemiplimab, resulting in a significant clinical response as per RECIST criteria. The diverse responses highlight the potential but inconsistent efficacy of ICIs in transplant recipients, affected by factors like previous immunosuppression, the biological features of each type of cancer, and underlying immune regulatory mechanisms [3, 9]. Delyon et al. performed an extensive review and case series about the use of ICIs in solid organ transplant recipients. Their examination of 91 cases, which includes their cohort of five patients, demonstrated that the overall response rates to ICI therapy exhibited considerable variation among distinct cancer types—36% in melanoma, 29% in hepatocellular carcinoma, 14% in non-small cell lung cancer, and 60% in cutaneous squamous cell carcinoma. Nevertheless, the prognosis for transplant recipients undergoing ICI therapy remained unfavorable, with 68% mortality attributed to cancer progression, which was the predominant cause of death, impacting 51% of patients.

In terms of graft survival, kidney transplant recipients demonstrated the highest acute rejection rate at 45%, followed by liver transplant recipients at 36%, and heart transplant recipients at 17%. Rejection rates were significantly elevated in patients administered anti-PD-1/PD-L1 drugs (44%) in contrast to those undergoing anti-CTLA-4 therapy (29%). The median duration from the commencement of immune checkpoint inhibitors to rejection was 22 days, primarily characterized by vascular rejection (Banff Grade 2A or higher) [3]. The significance of managing immunosuppression was emphasized, indicating that mTOR inhibitors may decrease the likelihood of rejection while preserving some tumor response; nevertheless, their overall effectiveness is still ambiguous, as a 35% rejection rate has been noted in patients receiving these inhibitors [3]. Barbir et al. conducted a recent review of immune checkpoint inhibitor medication in kidney transplant recipients, highlighting the associated risks and benefits [1]. Previous investigations suggested elevated rejection rates (40%-50%); however, current

prospective trials have demonstrated reduced rates (0%-12%), indicating that modifications in immunosuppression before initiating ICI therapy could mitigate these concerns. Despite reservations regarding diminished efficacy in immunosuppressed patients, the response rates for advanced skin malignancies in kidney transplant recipients were comparable to those in the non-immunosuppressed cohort. Their findings underscore the necessity of addressing oncologic advantages alongside graft longevity through meticulous immunosuppressive management, taking into consideration patients' preferences and their understanding of the risk of losing their grafted organs. The review promotes a multidisciplinary approach and additional research to refine immunosuppressive methods, boost patient monitoring, and enhance oncologic outcomes while maintaining graft function [1].

3.3. Strategies to Optimize ICI Use in Transplant Recipients

Given the significant rejection risk, optimizing immunosuppression in transplant recipients undergoing ICIs therapy is crucial. An observational study conducted by Dolladille et al. analyzed the safety of ICI rechallenge in cancer patients who had experienced immune-related adverse events (irAEs). The study, based on case reports from the World Health Organization VigiBase, found a 28.8% recurrence rate of irAEs after ICI rechallenge, with colitis, hepatitis, and pneumonitis being the most frequently recurring adverse events. These findings highlight the need for careful immunosuppressive management in transplant recipients receiving ICI therapy [10].

Given the high risk of rejection, strategies to optimize immunosuppression are crucial for success. Some evidence suggests that switching from CNI to mTOR inhibitors could help balance oncologic efficacy with graft preservation. Additionally, early corticosteroid administration, monitoring of donor-specific antibodies (DSAs), and regular assessments of renal function may enhance patient outcomes. Future research should explore personalized immunosuppressive approaches, including biomarkers for predicting rejection risk and strategies to maximize ICI benefits while minimizing complications [10]. Given the significant risk of rejection, optimizing immunosuppression strategies is crucial for effective treatment. Some evidence suggests that switching from CNI to mTOR inhibitors may help balance oncologic efficacy with graft preservation. However, this approach may be limited by adverse events associated with mTOR inhibitors, such as acute rejection, infection, and proteinuria, indicating that conversion therapy may only be suitable for selected patients [11].

According to a Consensus Report with Guideline Statements for Clinical Practice, published in 2023 by Dennis et al., the early administration of corticosteroids or other immunomodulators, combined with close monitoring of DSAs and renal function, may improve patient outcomes. Regular monitoring of DSAs in stable kidney transplant recipients can help identify patients at risk of antibody-mediated rejection and graft failure, allowing for timely interventions. Future research should explore personalized immunosuppressive approaches, including biomarkers for predicting rejection risk and strategies to maximize ICI benefits while minimizing complications [12].

Future research should focus on personalized immunosuppressive approaches, including the use of novel biomarkers to predict rejection risk and strategies to maximize the benefits of ICI therapy while minimizing complications.

3.4. Limitations and Future Directions

This case series is subject to several limitations. First, it represents a small, retrospective sample of four patients from a single center, which limits generalizability and prevents definitive conclusions regarding causality or treatment efficacy. Additionally, the follow-up period varied among cases and was relatively short in some, limiting the assessment of long-term graft survival and oncologic outcomes. Much of the clinical data, including treatment response and symptom burden, relied on retrospective chart review, which may be subject to incomplete documentation and recall bias. Finally, immunosuppressive adjustments were individualized based on clinician judgment, introducing heterogeneity that may affect the interpretation of results. Despite these limitations, the report provides valuable insights into the real-world challenges and outcomes faced by a clinically vulnerable population. Future prospective studies with standardized immunosuppressive protocols and biomarker-driven monitoring are needed to improve outcomes in this vulnerable population.

4. Conclusion

This case series highlights the concurrent issue of treating cancer and preventing graft rejection in kidney transplant recipients undergoing treatment with ICIs. ICI therapy can provide significant oncologic advantages, but it carries a considerable risk of immune-mediated graft malfunction or even rejection. Additional research is required to enhance immunosuppressive approaches, reduce rejection risk, and improve therapeutic outcomes in this particular patient population.

Conflicts of Interest

The authors declare no conflicts of interest related to this manuscript.

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Large Language Model

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Authors Contribution

All co-authors contributed equally to the conception, drafting, and revision of this article.

Data Availability

Data supporting the findings of this study are not publicly available but can be obtained from the corresponding author upon reasonable request.

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ASIDE Case Reports

Case Report

Amiodarone-Induced Thyrotoxicosis Presenting as Congestive Heart Failure Exacerbation and Thyroid Storm: Role of Plasmapheresis in Management and Prevention of Complications

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ABSTRACT

Amiodarone-induced thyrotoxicosis (AIT) is a subtype of thyrotoxicosis caused by the long-term administration of the antiarrhythmic drug amiodarone. It's classified into type 1 AIT, which is defined as hypersecretion of the thyroid hormone, while type 2 AIT is destructive thyroiditis leading to increased release of thyroid hormone. Each type has its special management and diagnostic features. We report a case of a 72-year-old male with a history of heart failure with reduced ejection fraction (HFrEF) and type 2 diabetes mellitus (DM) who presented with congestive heart failure (CHF) exacerbation and symptoms of an impending thyroid storm. After the diagnosis of type 2 AIT, medical treatment, as well as plasmapheresis, was initiated. In further admissions, the patient returned with ventricular tachycardia and right subclavian deep venous thrombosis due to recurrent catheterization and a hypercoagulable state. The diagnostic workup revealed elevated free T4, suppressed TSH, and initially elevated AST and ALT, which normalized subsequently. Imaging showed decreased thyroid vascularity. This case report highlights the importance of distinguishing between AIT types, tailoring optimal treatment decisions, closely monitoring and following up on such cases, and adhering to treatment to prevent catastrophic complications. Further research is necessary to identify early markers of amiodarone toxicity to prompt early diagnosis and better prognosis.

1. Introduction

Amiodarone, a benzofuranic iodine-enriched agent, contains approximately 37.5% iodine by weight [1]. It is a commonly used antiarrhythmic medication for both ventricular arrhythmias and paroxysmal atrial tachycardia [2, 1]. It is particularly used in patients with complicated and uncontrolled conditions who require standard treatment regimens [1]. However, it is well known for its life-threatening adverse events (AEs) [1]. These AEs are related to amiodarone because its chemical structure resembles thyroxine (T4), enabling it to bind to thyroid receptors [3]. As a result, it leads to either thyrotoxicosis [amiodarone-induced thyrotoxicosis] (AIT) or hypothyroidism, which doesn't pose significant strains [3].

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However, AIT is a highly fatal adverse event, especially for cardiac patients [3]. AIT is commonly mistaken for spontaneous hyperthyroidism, as not all individuals exhibit thyrotoxicosis symptoms and signs [3]. An exacerbation of an underlying cardiac disease could also mask it. These manifestations may include worsening of cardiac arrhythmia, recurrence of atrial fibrillation, palpitations, or the development of angina [3].

AIT is subclassified into AIT types 1 and 2, which have different underlying pathophysiology, as shown in **(Table 1)** [3]. AIT 1 commonly occurs in conjunction with thyroid disease, such as latent Graves' disease or multinodular goiter, leading to increased thyroid hormone production due to a sudden increase in iodine intake; herein, AIT type 1 is more common in patients with low dietary iodine intake [4]. However, AIT type 2 is more frequent than AIT type 1, resulting in amiodarone toxicity, which can damage the thyroid gland, leading to the release of pre-formed hormones without an increase in hormone biosynthesis [5].

It's essential to distinguish between them, as their treatment regimens differ. AIT 1 is commonly associated with an enlarged thyroid gland, typically characterized by a low T4/T3 ratio (<4), elevated thyroid blood flow on Doppler ultrasound, and high iodine uptake levels on a thyroid scan [6]. Thus, the treatment regimen could be antithyroid drugs such as methimazole or propylthiouracil. While AIT 2 develops in healthy patients without underlying thyroid diseases and is presented with a normal or atrophic thyroid gland, it

Table 1: Comparison of Amiodarone-Induced Thyrotoxicosis (AIT) Type 1 and Type 2

Feature	AIT Type 1	AIT Type 2
Cause	Underlying thyroid disease (e.g., multinodular goiter, Graves' disease)	Direct thyroid destruction by amiodarone toxicity
Pathophysiology	Increased thyroid hormone synthesis	Thyroid follicular cell damage and release of thyroid hormones
Pre-existing Thyroid Condition	Often in patients with pre-existing thyroid disease	Usually occurs in a previously normal thyroid
Onset	Gradual	Sudden
Radioiodine Uptake (RAIU)	Normal or increased	Low or absent
Doppler Ultrasound	Increased vascularity (hypervascularity)	Decreased vascularity (hypovascularity)
Serum IL-6 Levels	Normal or mildly elevated	Markedly elevated
Response to Therapy	Poor response to corticosteroids; responds to thionamides (methimazole, propylthiouracil)	Responds well to corticosteroids; poor response to thionamides
Treatment Options	- Thionamides (Methimazole, PTU) - Potassium perchlorate (to reduce iodine uptake) - Sometimes, plasmapheresis or surgery is required in severe cases	- High-dose corticosteroids (prednisone) - Supportive treatment until resolution
Prognosis	May require long-term treatment or thyroidectomy	Usually self-limited, resolves with corticosteroids

AIT, Amiodarone-Induced Thyrotoxicosis; RAIU, Radioiodine Uptake; IL-6, Interleukin-6; PTU, Propylthiouracil

usually has a high T4/T3 ratio (>4) and low iodine uptake. As AIT 2, or destructive thyroiditis, has an ongoing inflammatory process, its effective treatment is glucocorticoids [6].

In this case report, we describe the challenging journey of an old man with heart failure and other comorbidities who developed AIT. So, he required urgent efforts to reduce serum thyroxine to prevent cardiac decompensation. With persistent ambiguity around the AIT subtype, we successfully restored the euthyroid state with a combination of methimazole and prednisone.

2. Case Presentation

A 72-year-old male with no prior history of thyroid disease presented to the Emergency Department (ED) with generalized weakness, shortness of breath, and increased confusion. He was admitted to acute on top of chronic congestive heart failure (CHF) and was diagnosed with severe hyperthyroidism based on abnormal thyroid function tests (TFTs). His past medical history includes heart failure with reduced ejection fraction (EF 10-20%) 1 year ago, coronary artery disease with a prior non-ST-elevation myocardial infarction (NSTEMI) 2 years ago, ischemic cardiomyopathy, type 2 diabetes mellitus, atrial fibrillation, and a Factor V Leiden mutation. The patient had been on amiodarone for one year but stopped the medication two months prior due to insurance issues.

The patient presented to the ED with generalized weakness, shortness of breath, confusion, and vomiting. He had stopped taking amiodarone two months prior due to insurance issues. His vital signs upon arrival were a temperature of 98.1°F, a heart rate of 94 beats per minute (bpm), a blood pressure of 121/60 mmHg, and an SpO2 of 91% on room air. Physical examination showed no signs of a goiter, clear lung fields, a regular heart rhythm, a non-tender abdomen, no conjunctival injection, no scleral icterus, and moist oral mucosal membranes. As seen in **(Table 2)**, pertinent laboratory tests upon admission revealed significantly elevated free T4 (7.7 ng/dL), suppressed TSH (<0.1 μIU/mL), and markedly elevated liver enzymes (AST/ALT in the 300s), consistent with amiodarone-induced thyrotoxicosis and impending thyroid storm. Thyroid antibodies were pending to further differentiate the type of AIT. The Burch-Wartofsky Point Scale (BWPS) indicated an impending thyroid storm. Final diagnoses included Type II amiodarone-induced thyrotoxicosis, impending thyroid storm, and acute-on-chronic CHF. Management included cholestyramine (4 g QID), beta-blockers (titrated to HR 60–90 bpm), hydrocortisone (100 mg q8 h), and insulin for steroid-induced hyperglycemia. Plasmapheresis was initiated with a central line, and the first session on day 2 after admission reduced Free T4 from 7.7 to 5.32. LFTs improved, and the patient was discharged with weekly TFT/LFT monitoring and continued medications. The family confirmed that they would be available to help the patient with insulin injections if needed. The patient is also learning how to give himself insulin, as he may need to be on a higher dose of insulin for some time since he is on high-dose steroids for AIT. The patient continued cholestyramine (4 g) four times daily, prednisone 60 mg daily, and a beta-blocker, titrating the dose to maintain a heart rate of less than 90 beats per minute.

Two months later, the patient was readmitted with a recurrent exacerbation of CHF and ventricular tachycardia (VT). Vital signs included a temperature of 97.8 °F, heart rate of 82 bpm, blood pressure of 110/83 mmHg, and SpO2 of 100%. The physical examination findings were consistent with previous admissions and showed no significant changes. As seen in **(Table 2)**, laboratory tests during the second admission showed persistently elevated free T4 (7.38 ng/dL), suppressed TSH (<0.1 μIU/mL), and mildly elevated liver enzymes (AST 49 U/L, ALT 90 U/L), indicating ongoing thyrotoxicosis and the need for continued aggressive management. Recurrent V. tach episodes and persistently elevated Free T4 (>7.77) prompted the initiation of methimazole (60 mg daily, increased to 90 mg on 10/24) and the continuation of p.o. Prednisone (60 mg daily). Cholestyramine was discontinued due to non-compliance. The patient underwent his first session of plasmapheresis on October 18. After the first plasmapheresis session, his thyroid hormone levels improved but gradually increased to approximately 6.75 (free T4). We conducted another plasmapheresis session on October 24, resulting in an immediate improvement in free T4 levels. We discontinued cholestyramine on 10/24 since the patient was not getting the medications as recommended. Post-TPE, LFTs normalized, and the patient was discharged on methimazole

Table 2: Laboratory Investigations

Test	Result	Normal range
First admission		
Free T4	7.7	0.8–1.8 ng/dL
TSH	0.01L	0.4–4.0 μIU/mL
Second admission		
Free T4	7.38	0.8–1.8 ng/dL
TSH	<0.01	0.4–4.0 μIU/mL
AST	49 U/L	10–40 U/L
ALT	90 U/L	7–56 U/L
Third admission		
Free T4	5,14	0.8–1.8 ng/dL
Free T3	2.9	2.3–4.2 pg/mL
TSH	<0.01	0.4–4.0 μIU/mL

Free T4, Free Thyroxine; Free T3, Free Triiodothyronine; TSH, Thyroid-Stimulating Hormone; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase;

(90 mg daily), prednisone (60 mg daily), and beta-blockers, with plans for outpatient TPE as needed.

After a month, the patient was admitted with right shoulder pain due to deep vein thrombosis (DVT), requiring intravenous heparin. As seen in (**Table 2**), Thyroid function tests revealed a Free T4 level greater than 5.14 ng/dL, suppressed TSH, and normal Free T3 at 2.9 pg/mL. A neck ultrasound with Doppler imaging showed decreased thyroid vascularity, which supported a diagnosis of Type II AIT. Management included continued methimazole (90 mg daily), prednisone (60 mg daily), and IV heparin for DVT. Goals of care discussions reaffirmed the family's refusal of thyroidectomy. Outpatient TPE was deemed feasible for future hormone surges.

3. Discussion

The severe amiodarone-induced thyrotoxicosis (AIT), end-stage heart failure, and other multiple comorbidities are what make this 72-year-old male a challenging case to manage, especially when traditional treatments are contraindicated or insufficient.

Although the amiodarone was discontinued two months before, this did not prevent thyrotoxicosis. Amiodarone has an extremely long half-life (approximately 100 days) due to its lipophilic nature and extensive tissue distribution. This explains why thyrotoxicosis can develop even months after discontinuation, as the drug continues to be released from tissue stores. Studies have shown that AIT can occur in 3-5% of amiodarone-treated patients in iodine-sufficient areas and up to 10% in iodine-deficient regions[6].

Amiodarone partially exerts its antiarrhythmic effects by suppressing the Type 1 5-deiodinase enzyme, which inhibits the conversion of T4 to T3 in peripheral tissues. Additionally, its active metabolite, desethylamiodarone (DEA), can cause direct thyroid cell damage at high concentrations, leading to both hyperthyroidism and hypothyroidism based on individual vulnerability [7]. The key to effective diagnosis and management is the accurate differentiation between Type 1 and Type 2 AIT. The patient showed reduced thyroid vascularity on color flow Doppler sonography, which supports the diagnosis of Type 2 AIT, linked to drug-induced thyroiditis rather than increased hormone production. The absence of thyroid antibodies (pending but likely negative given the clinical course) further supports Type II AIT, as autoimmunity is more characteristic of Type I disease. Type 2 AIT is seen in iodine-deficient regions and doesn't necessitate pre-existing thyroid disease. Unlike Type 1 AIT, which occurs more frequently in areas with high iodine levels, Type 2 AIT is seen in iodine-deficient regions and doesn't necessitate pre-existing thyroid disease [8].

As amiodarone therapy can induce a delayed onset of Type 2 AIT even years after the initial treatment course, ongoing TFT is needed for follow-up, especially in high-risk individuals. The patient's failure to attend follow-up visits leads to a delay in diagnosis and intervention, which causes the progression of severe thyrotoxicosis [2, 9]. Generalized weakness, shortness of breath, confusion, and vomiting were the initial presentation, which raised concerns for an impending thyroid storm, confirmed by the BWPS. Elevated free T4 (7.7 ng/dL) and suppressed TSH (<0.1 μIU/mL) confirmed the diagnosis, requiring immediate intervention. Similar cases have been reported where AIT Type 2 manifested as a thyroid storm, often complicating underlying cardiac conditions [10].

As thyroid storm is a life-threatening complication, the first aim of management is to control plasma thyroid levels and its related symptoms. Patient's elevated liver enzymes and ineligibility for surgery made conservative management the best choice for him. Cholestyramine was used to bind thyroid hormones in the gut, thereby limiting recirculation; however, its effectiveness was compromised by the patient's non-compliance [11]. To stabilize the heart rate within the range of 60-90 bpm and manage adrenergic symptoms, beta blockers were used. Hydrocortisone was utilized to control steroid-induced hyperglycemia and address the inflammation linked to Type 2 AIT [12]. Plasmapheresis emerged as an essential intervention, significantly reducing free T4 levels during the acute crisis [13]. This is consistent with prior research demonstrating substantial reductions in free T4 and T3 after multiple sessions of therapeutic plasma exchange (TPE) [14]. Methimazole and prednisone were introduced subsequently, leading to the successful and sustained normalization of thyroid function despite the patient's hepatic limitations [15]. Methimazole is considered the treatment of choice for antithyroid therapy due to its effectiveness and relatively low side-effect profile. However, regular liver function tests (LFTs) are necessary to identify any signs of hepatotoxicity early on [16].

During the second admission, the patient developed VT, further emphasizing the critical cardio-endocrine connection in AIT Type 2. Previous studies have highlighted similar cases in which uncontrolled thyrotoxicosis triggered arrhythmias, reinforcing the necessity of regular TFT follow-up with established guidelines [17, 18, 19, 20]. Beta-blocker usage and plasmapheresis were necessary to stabilize the patient's rhythm and avoid further complications.

After undergoing several cycles of plasmapheresis, the patient developed a right subclavian DVT. This condition treatment aligns with the hypercoagulable state associated with thyrotoxicosis induced using central venous catheters, further aggravated by a factor V Leiden mutation. Risk of venous thromboembolism increased by 1.55-fold in hyperthyroid patients compared to controls in a population-based cohort study of 12,844 patients [21]. In response, anticoagulation therapy with intravenous heparin was initiated to reduce the risk of thromboembolism. The definitive treatment for refractory AIT is thyroidectomy, which offers quick normalization of thyroid hormone levels and enhances cardiac performance [22]. However, the patient's family refused to undergo surgery due to concerns about the potential risks in his fragile condition [23].

Their decision highlights the ethical challenges of recommending invasive procedures for high-risk elderly patients.

Patient-centered care principles often favor conservative measures over surgery. These conservative measures focus on symptom relief and enhancing quality of life. While these approaches successfully manage immediate symptoms, they may potentially delay the resolution of underlying thyroid dysfunction, which could negatively affect long-term outcomes [22]. Future research is needed to develop strategies that optimize outcomes for similar high-risk patients, taking into account efficacy, safety, and patient preferences.

4. Conclusion

Plasmapheresis provided rapid hormonal control in emergent cases, while respecting patient preferences was essential for improving adherence and quality of life. Future studies should focus on personalized treatment strategies for high-risk populations to enhance outcomes.

Conflicts of Interest

The authors declare that they have no competing interests.

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Large Language Model

None

Authors Contribution

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Data Availability

Patient data related to this study are not publicly available but can be obtained upon request from the corresponding author.

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