Volume 1, Issue 2, (2025)

1st December, 2025

DOI.org/10.71079/ASIDE.CR.1.2

ASIDE HEALTHCARE CASE REPORTS

PUBLISHED BY
AMERICAN SOCIETY FOR INCLUSION, DIVERSITY, AND EQUITY IN HEALTHCARE (ASIDE)

ISSN (Print) 3066-7224
ISSN (Online) 3066-7232

Index

ASIDE Case Reports

Case Report

Hybrid Schwannoma of the Nasal Cavity: A Rare Case Report with Literature Review

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ARTICLE INFO

Article history:
Received 8 May. 2025
Received in revised form 25 May. 2025
Accepted 13 Jun. 2025
Published 16 Jun. 2025

Keywords:
Schwannoma
Nasal cavity
Epistaxis
Endoscopic sinus surgery
Case report

ABSTRACT

Sinonasal schwannomas are extremely rare, comprising only 4% of all head and neck schwannomas. Their atypical location and nonspecific symptoms often result in delayed diagnosis. This case highlights a rare hybrid schwannoma in the right nasal cavity of a young female, contributing to the limited literature on sinonasal nerve sheath tumors. A 27-year-old female presented with a one-year history of right-sided nasal obstruction, rhinorrhea, and recurrent epistaxis. Examination revealed a polypoidal mass in the right nasal cavity. Laboratory investigations showed mild anemia and an elevated white cell count. Imaging identified a soft tissue mass with no bone erosion or intracranial involvement. The patient underwent Functional Endoscopic Sinus Surgery (FESS), and histopathological analysis confirmed a hybrid nerve sheath tumor (70% schwannoma, 30% neurofibroma) with positive staining for S-100 and CD34. Postoperative MRI showed no residual or recurrent mass. This case underlines the importance of considering rare neural tumors in the differential diagnosis of nasal masses. Early surgical intervention with histological confirmation ensures favorable outcomes and prevents complications associated with delayed treatment.

1. Introduction

Schwannomas are rare benign tumors that originate from Schwann cells and are responsible for producing the myelin sheath around peripheral nerves. They typically affect middle-aged adults without preference for gender or ethnicity and can occur throughout the body, with around 45% of schwannomas arising from the head and neck region. Of these, only about 4% arise in the nasal cavity and paranasal sinuses. Symptoms of sinonasal schwannomas are often nonspecific and may include nasal obstruction, epistaxis, rhinorrhea, anosmia, headache, or facial swelling, leading to delayed diagnosis. Surgical removal is the treatment of choice, and a definitive diagnosis is confirmed through histopathological examination [1, 2].

These benign, well-encapsulated tumors originate from Schwann peripheral nerve sheath cells. Recurrence following surgical removal is uncommon.[3] Despite originating from a single cell type, schwannomas can exhibit a wide range of cellular morphologies. Variants include cellular, cystic, ancient, epithelioid, melanotic, pseudo glandular, psammomatous, and plexiform forms [4, 5].

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Published in collaboration with the American Society for Inclusion, Diversity, and Equity in Healthcare (ASIDE). ISSN (Print) 3066-7224, ISSN (Online) 3066-7232 – see front matter

Citation: Rafique A, Adeel MU, Sultan R, et al. Hybrid Schwannoma of the Nasal Cavity: A Rare Case Report with Literature Review. ASIDE Case Reports. 1(2):1-5, doi:10.71079/ASIDE.CR.061625103

Polypoid lesions in the nasal cavity are commonly of inflammatory origin, whereas nerve sheath tumors are rarely encountered in this region. These tumors typically originate from branches of the trigeminal nerve. Pathologists should recognize this uncommon presentation; thorough evaluation is essential to rule out malignant potential [6].

What makes this case especially noteworthy is the discovery of a hybrid schwannoma—a rare tumor made up of both schwannomatosis and neurofibromatosis components—located in the right nasal cavity of a young woman [7].Tumors like this are extremely uncommon in this part of the body and can easily be mistaken for more typical nasal conditions, such as polyps, making diagnosis challenging. By sharing this case, we aim to highlight its unusual presentation and key clinical, imaging, surgical, and histological findings to help other clinicians recognize and manage similar cases more effectively.

2. Case Presentation

The patient is a 27-year-old woman of Punjabi descent who came to the ENT department with a one-year history of right-sided nasal obstruction, ongoing nasal discharge, and frequent episodes of nosebleeds. She had no previous history of sinus-related conditions such as chronic sinusitis, asthma, or allergic rhinitis, and she was not taking any regular medications. There were no known allergies, including common triggers like aspirin or NSAIDs, and no signs of immunodeficiency disorders such as Churg-Strauss syndrome. Her family history was unremarkable, with no relatives affected by similar nasal issues, neurofibromatosis, or hereditary conditions

like cystic fibrosis. Socially and psychologically, there were no notable concerns, and she had not undergone any previous surgeries or medical treatments related to her current symptoms.

The patient was alert, oriented, and vitally stable, with no signs of systemic illness or skin lesions suggestive of neurofibromatosis. An anterior rhinoscopy showed a fleshy, polypoidal mass in the right nasal cavity, extending from the inferior to the medial wall. The mass appeared vascular and non-friable. The nasal septum was deviated to the left, with a visible septal spur**(Figure 1)**.

Posterior rhinoscopy was unremarkable. Ear and throat examinations were normal, with intact tympanic membranes and a clear oropharynx. There was no cervical lymphadenopathy, and neurological examination showed no deficits.

Blood samples were taken and sent for baseline laboratory analysis, which yielded the following results. The patient was given the choice to send her blood samples to either our institute's laboratories or some other laboratory, and she opted for the latter Section 2. Pre-operative imaging, including a CT scan of the paranasal sinuses, was performed (prior to her presentation with our team) without contrast using axial slices of 3 mm thickness and reformatted coronal slices. The findings revealed bilateral mild mucosal thickening in the maxillary and ethmoid sinuses. A soft tissue opacity was noted in the right lower nostril, measuring approximately 2.1 × 1.6 cm. A deviated nasal septum (DNS) was also identified, with convexity toward the left side and a small spur. There was no evidence of intracranial or intraorbital extension, and no signs of bone erosion were observed. The impression was bilateral maxillary and ethmoid sinusitis and a soft tissue opacity in the right lower nostril, for which clinical correlation was advised. Multiple differential diagnoses for the nasal mass were considered based on the examination and imaging findings. Neoplastic lesions such as inverted papilloma, hemangioma, and nasopharyngeal angiofibroma. Inflammatory or reactive conditions like chronic inflammatory polyps and fungal sinusitis. Structural abnormalities such as turbinate hypertrophy and encephalocele. As such, histopathological evaluation remained essential for confirmation and further treatment management.

This patient's treatment was performed in a state-of-the-art tertiary care hospital in Lahore, Pakistan, with access to diagnostic modalities such as CT scan, MRI, and a well-equipped pathology lab. However, the patient was allowed to use the diagnostic services of other hospitals. She opted to utilize the services of the nearest government-funded hospital, whichprovides subsidized rates for these diagnostic modalities.

The patient, with ongoing symptoms, was scheduled for Functional Endoscopic Sinus Surgery (FESS) and septoplasty. Endoscopic surgery has been mostly reported in the recent 20 years and is becoming the most widely used procedure. Even in extensive diseases, no recurrence is reported after endoscopic surgery.[8] In the past, more invasive transcranial and transfacial methods were employed for removal but are employed for those tumors which have undergone malignant transformation.[9] During surgery, a polypoidal vascular mass was found in the right nasal cavity, attached to the lateral wall above the inferior turbinate. Hemostasis was achieved, after which the mass was removed, and the nasal cavity was packed. A sample was sent for histopathological analysis. A surgical pathology examination was performed on the mass excised from the right nasal cavity at Aga Khan Laboratories, a state-of-the-art tertiary hospital in Pakistan. Gross examination described a single, soft, polypoidal tan-white to tan-brown tissue measuring 2.6 × 2.2 cm. Microscopically, the mucosa-covered tissue showed a neoplastic lesion composed of short fascicles and nests with alternating hypercellular and hypocellular areas. The neoplastic cells had hyperchromatic nuclei, inconspicuous nucleoli, and moderate cytoplasm. A few mitotic figures were noted, and the stroma appeared collagenous. Some cellular areas showed typical Verocay body formation. Interspersed, thin-walled blood vessels

Table 1: Laboratory Parameter Trends Over Time

Parameter	pre surgery	post surgery	Reference Range / Normal
White Blood Cells (WBCs) ($\times 10^9$/L)	8.7	10.3	4.0 – 10.0
Neutrophils (%)	45	60	40 – 75
Lymphocytes (%)	50	30	20 – 50
Eosinophils (%)	3	6	1 – 6
Monocytes (%)	2	4	2 – 10
Hemoglobin (Hb) (g/dL)	11.8	10.5	12.0 – 16.0
Red Blood Cell Count (RBC) ($\times 10^{12}$/L)	4.73	4.00	4.0 – 5.50
Hematocrit (Hct) (%)	40.3	34.3	40.0 – 54.0
Mean Corpuscular Volume (MCV) (fL)	85.2	85.8	80.0 – 100.0
Mean Corpuscular Hemoglobin (MCH) (pg)	24.9	26.3	27.0 – 34.0
MCH Concentration (MCHC) (g/dL)	29.3	30.6	32.0 – 36.0
RDW-CV (%)	14.4	14.3	—
RDW-SD (fL)	12.5	8.7	11.5 – 14.5
MPV (Mean Platelet Volume) (fL)	10.0	11.9	7 – 11
Platelet Count ($\times 10^9$/L)	325	422	150 – 450
PT (Prothrombin Time) (sec)	13	—	12 – 15
INR	0.93	—	∼1.0 (normal, non-anticoagulated)
APTT (sec)	36	—	30 – 45
HBs Ag	Negative	—	Negative
HCV	Negative	—	Negative
Blood Urea (mg/dL)	—	27	10 – 50
Serum Creatinine (mg/dL)	—	0.93	0.6 – 1.2 (Female)

WBCs, White Blood Cells; Hb, Hemoglobin; RBC, Red Blood Cell Count; Hct, Hematocrit; MCV, Mean Corpuscular Volume; MCH, Mean Corpuscular Hemoglobin; MCHC, Mean Corpuscular Hemoglobin Concentration; RDW-CV, Red Cell Distribution Width-Coefficient of Variation; RDW-SD, Red Cell Distribution Width-Standard Deviation; MPV, Mean Platelet Volume; PT, Prothrombin Time; INR, International Normalized Ratio; APTT, Activated Partial Thromboplastin Time; HBs Ag, Hepatitis B Surface Antigen; HCV, Hepatitis C Virus.

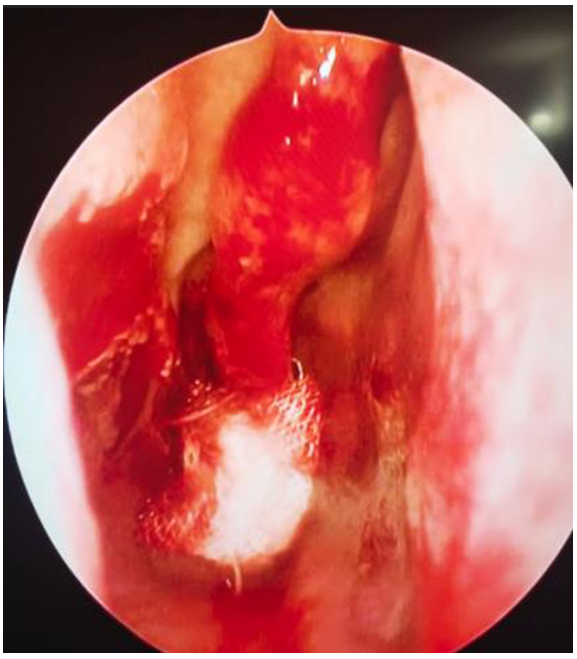

Figure 1: Endoscopic view showing a polypoidal vascular mass in the right nasal cavity, attached to the lateral wall above the inferior turbinate

were present. There was no evidence of increased mitoses, cytological atypia, or sarcomatous transformation. Immunohistochemical staining showed positivity for CD34 and S100, while TLE-1 was negative. The diagnosis concluded that the lesion was a polypoid vascular mass identified as a hybrid nerve sheath tumor, composed of 70% schwannoma and 30% neurofibroma, with no malignant features.

The patient recovered well following surgery, with no immediate postoperative complications. She reported significant relief from her symptoms, including complete resolution of nasal obstruction and nosebleeds, and remained clinically stable. As part of her follow-up, the case was reviewed in a multidisciplinary team meeting, and a contrast-enhanced MRI was performed six weeks later to assess for any residual tumor. The MRI revealed no enhancing soft tissue mass in the nasal cavity, confirming successful tumor excision. The absence of the right inferior turbinate was consistent with surgical removal. Mild mucosal thickening was seen in both maxillary sinuses, with a slightly thickened area along the superior wall of the left maxillary sinus, measuring 5mm in thickness, suggesting sinusitis. Importantly, there was no evidence of intraorbital extension, and the adjacent anatomical structures appeared normal, including the orbits, salivary glands, and brain. The patient tolerated the MRI well, with no complications or unexpected adverse events, as the patient was not claustrophobic, and no technical issues were reported during the procedure. Overall, the follow-up findings supported a favorable outcome with no signs of recurrence. A summary of the clinical timeline is provided in Section 2.

3. Discussion

This case report gives a detailed clinical and histopathological analysis of a rare hybrid sinonasal schwannoma. It adds to the limited literature on hybrid schwannomas compared to nasal polyps, providing valuable insight into the differential diagnosis. Hybrid sinonasal schwannomas are extremely rare and can pose a real diagnostic challenge, such as when the schwannoma is suspected

Table 2: Timeline of Clinical Events and Interventions

Time	Event
12 months prior	Onset of right-sided nasal obstruction, rhinorrhea, and recurrent epistaxis
At presentation	Clinical evaluation, nasal endoscopy, and lab tests were performed. CT scan of paranasal sinuses revealed the right nasal mass and DNS.
Scheduled surgery	Underwent Functional Endoscopic Sinus Surgery (FESS) with septoplasty
Post-op (6 weeks)	MRI was performed to evaluate residual disease; no recurrent mass was observed

DNS, Deviated Nasal Septum; FESS, Functional Endoscopic Sinus Surgery; MRI, Magnetic Resonance Imaging; CT, Computed Tomography.

to originate from the sphenopalatine or lateral nasal branches of the maxillary nerve. There are many instances in medical literature of hybrid schwannomas being of dermal or subdermal origin, thus making them uncommon in the sinonasal region [10]. Hence, their presence near the sphenopalatine foramen and maxillary nerve branches demands careful evaluation and detailed histopathological analysis. What makes hybrid schwannomas particularly tricky is their mixed composition—about 60 to 70% schwannomatous, which stain S-100 and SOX10 positive and the remainder 30 to 40% perineural cells staining claudin 1 and GLUT1-positive—often leading to misidentification as more common sinonasal tumors [11, 7]. Recognizing them early is crucial, as delayed diagnosis can result in worsening nasal obstruction, persistent facial pain, and even orbital involvement, significantly affecting a patient's quality of life.

Schwannomas are benign peripheral nerve sheath tumors first described by José Juan Verocay in 1910. These tumors typically affect individuals aged 40 to 60, though they can occur at any age, with a peak incidence between 2 and 81 years [12]. Nasal cavity schwannomas are rare, constituting only 4% of sinonasal tumors. They are predominantly female (F: M ratio 1.8:1) [13]. Most schwannomas in the head and neck arise from the trigeminal nerve, and they are rarely seen in the nasal cavity or paranasal sinuses, including the ethmoid, maxillary, and sphenoid sinuses [14].

Histopathologically, schwannomas are classified into Antoni-A and Antoni-B types. Antoni-A areas have dense, organized stroma with spindle-shaped cells and rows of nuclei arranged in a palisading pattern, known as Verocay bodies. Antoni-B areas consist of a looser myxoid stroma with fewer spindle cells[15, 12, 16]. Schwannomas are strongly associated with neurofibromatosis type 2 (NF2), which commonly affects the vestibular nerve, while neurofibromatosis type 1 (NF1) is more linked to neurofibromas [17]. NF2 results from mutations in the NF2 gene, whereas mutations in the NF1 gene cause NF1. S-100 staining is essential for diagnosing schwannomas, as both schwannomas and neurofibromas react, but schwannomas show a stronger reaction. Calretinin and CD56 are more specific to schwannomas, while CD34 and factor XIIIa are sensitive to neurofibromas [15]. In this case, CD34 and S-100 were patchy positive, while TLE-1 was negative, though TLE-1's role in diagnosis is still being studied. Surgical resection is the main treatment for schwannomas [18, 19]. Approaches like midfacial degloving, lateral rhinotomy, or endoscopic surgery are used based on tumor location [6]. In this case, the mass was

removed via Functional Endoscopic Sinus Surgery (FESS) under general anesthesia.

Despite focusing on a rare case of sinonasal schwannoma, this study, being a single case report, is subjected to restricted generalizability, making it difficult to draw broader conclusions regarding hybrid schwannomas in the sinonasal region. Furthermore, the absence of long-term follow-up prevents a comprehensive assessment of recurrence risk and potential postoperative complications. Histopathological interpretation, despite confirming hybrid nerve sheath tumor features, remains subject to interobserver bias, which could influence classification accuracy. Additionally, imaging modalities were limited to CT and MRI, whereas functional imaging techniques such as PET scans might have provided further insights into tumor spread and metabolism. Another limitation is the lack of genetic analysis, as molecular studies on relevant mutations like NF1 or NF2 could enhance our understanding of the tumor's pathophysiology. Lastly, while Functional Endoscopic Sinus Surgery (FESS) was employed successfully, comparative data evaluating alternative surgical techniques would help contextualize treatment choices more effectively. These limitations emphasize the need for further research to refine diagnostic accuracy and optimize management strategies for hybrid schwannomas.

Considering the clinical picture, diagnosis, and follow-up, it is concluded that Schwannomas are benign, sex—and race-independent tumors that are rare in the head and neck and account for 4% of sinonasal cases. Diagnosis is confirmed via S-100 staining. In this case, the patient underwent FESS-assisted excision under general anesthesia and recovered without complications.

4. Conclusions

This case highlights the diagnostic challenge of hybrid sinonasal schwannomas, a rare entity often misidentified due to its mixed histological features. Accurate diagnosis relies on thorough histopathological and immunohistochemical analysis, particularly in lesions near the sphenopalatine foramen. Surgical excision via FESS proved effective, with an uncomplicated recovery. Despite its limitations, this report adds to the scarce literature and underscores the need for greater clinical awareness and further research into optimal diagnostic and management strategies.

Conflicts of Interest

The authors declare that they have no competing interests that could have influenced the objectivity or outcome of this investigation.

Funding Source

This Article did not receive any specific grant from public, commercial, or not-for-profit funding agencies.

Acknowledgments

None

Informed consent

Written consent was obtained from the patient to publish this case report and images. All relevant information and confidentiality rights were explained, and identifying details have been anonymized.

Large Language Model

None

Authors Contribution

All authors contributed equally to the manuscript, and all authors read and approved the final version of the manuscript.

Data Availability

All information presented in this case report is included within the manuscript. If further details are required, please contact the corresponding author.

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ASIDE Case Reports

Case Report

Epiploic Appendagitis Following Blunt Abdominal Trauma: A Case Report with Literature Review

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ARTICLE INFO

Article history:
Received 30 Apr. 2025
Received in revised form 25 May 2025
Accepted 8 Jun. 2025

Keywords:
Abdominal trauma
Acute abdomen
Appendage
Diverticulitis
Epiploic appendagitis

ABSTRACT

Epiploic appendagitis (EA) is a rare and self-limiting cause of acute abdominal pain resulting from ischemia due to torsion or venous thrombosis of epiploic appendages. It often mimics more common conditions, such as diverticulitis or appendicitis, leading to misdiagnosis and unnecessary interventions. While EA is typically idiopathic, we present a unique case of trauma-induced EA in a 58-year-old man who developed sharp left lower quadrant pain after prolonged abdominal pressure while repairing a boat engine managed conservatively, which, to our knowledge, has not been previously reported. With the increasing availability of computed tomography (CT), EA is being diagnosed more frequently, yet clear management guidelines remain lacking.

1. Introduction

Epiploic appendagitis (EA) is a rare manifestation of the acute abdomen that occurs primarily when venous vascular impairment caused by thrombosis or torsion leads to ischemia of the epiploic appendages surrounding the colonic surface. The incidence of EA is estimated to be approximately 8 cases per million cases annually. In addition, EA can be triggered as a secondary outcome of inflammation in a typically normal epiploic appendage near an inflamed organ such as the colon, gallbladder, or appendix [1]. EA lacks specific clinical features and can mimic other causes of acute abdomen, making its diagnosis difficult, but abdominal pain is the main symptom. A recent single-center retrospective study of 39 patients found that nearly 69% of subjects experienced abdominal pain, with 51% experiencing left lower quadrant tenderness [2]. Another study by Ozdemir et al. showed abdominal pain as the predominant symptom in all 12 patients, with 70% being left-sided. Notably, only two patients reported associated symptoms such as nausea, vomiting, and constipation [3]. Several risk factors are associated with EA, including male gender, age in the 4th to 5th decades of life, and obesity. For example, patients with EA had 60% greater abdominal adiposity than patients with other causes of acute abdomen; of these, 67% were male [4]. CT scan is the method of choice for diagnosing EA with a fatty ovoid lesion as the pathognomonic feature [2, 4, 5] As the majority of the literature supports conservative treatment of EA, it is crucial to accurately diagnose EA to avoid unwarranted interventions [2, 4]. To the best of our knowledge, we present the first trauma-induced EA in a 58-year-old man treated conservatively.

2. Case Presentation

A 58-year-old man with a history of hypertension and hyperlipidemia and a body mass index (BMI) of 26 presented to our outpatient clinic with abdominal pain for three days. The onset of symptoms occurred after the patient was positioned on his left side against a boat's edge for a 45-minute engine repair activity, thereby exerting pressure on the left abdominal region. Initial discomfort, characterized as mild soreness in the left lower quadrant, progressed to a sharp localized pain rated at 7/10 over the ensuing three days, accompanied by significant tenderness. The pain was exacerbated by movement and deep inspiration, and its intensity was alleviated by non-steroidal anti-inflammatory drugs (NSAIDs). He had no other symptoms, such as nausea, vomiting, fever, nor any changes in bowel movements or urination. There were no changes in appetite, and the pain was unrelated to food intake. Physical examination revealed guarding and tenderness in the left lower quadrant. Laboratory workup was normal.

A CT scan of the abdomen and pelvis showed a 2.5 x 1.3 cm ovoid, fat-density structure with a thin enhancing rim and central hyperdensity abutting the descending colon **(Figure 1)**. There were no colonic diverticula. Diagnosed with EA, the patient was advised to take NSAIDs. The pain resolved within eight days, with NSAID use limited to the first three days. At the six-month follow-up, the patient remained asymptomatic without recurrence.

3. Discussion

Epiploic appendages are fatty pouches that attach along the entire colon, which are prevalent in the sigmoid colon [4, 6, 5, 7]. The principal symptom of EA is focal abdominal pain that can occur in any quadrant of the abdomen but has been mainly reported

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Published in collaboration with the American Society for Inclusion, Diversity, and Equity in Healthcare (ASIDE). ISSN (Print) 3066-7224, ISSN (Online) 3066-7232 – see front matter

Citation: Obeid A, Degler D. Epiploic Appendagitis Following Blunt Abdominal Trauma: A Case Report with Literature Review. ASIDE Case Reports. 2025;1(2):6-9, doi:10.71079/ASIDE.CR.06192587

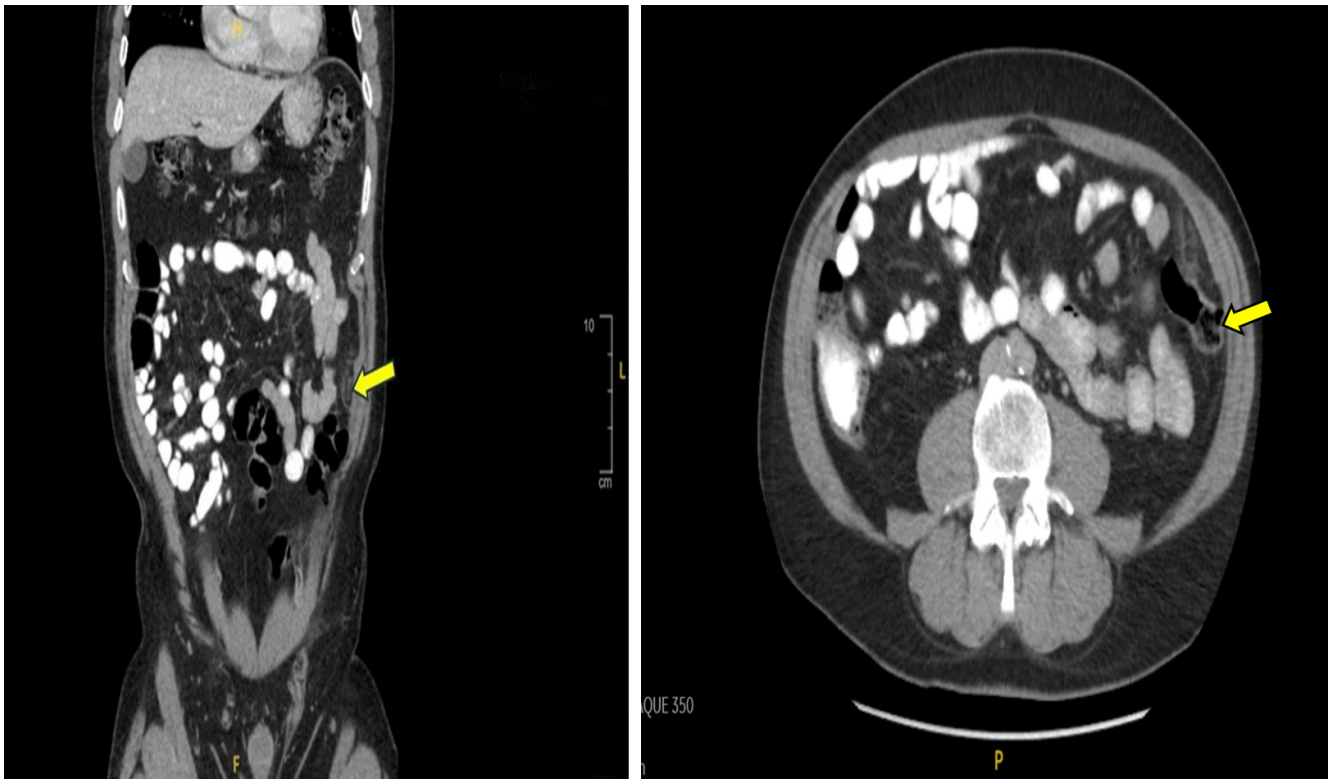

Figure 1: A 2.5 x 1.3 cm ovoid, fat-density structure with a thin enhancing rim and central hyperdensity abutting the descending colon.

on the left side, resembling diverticulitis [2, 3, 6, 8]. Associated symptoms include wide nonspecific symptoms such as nausea, vomiting, constipation, anorexia, and dysuria, which have been reported [9, 2, 10, 3, 6, 8]. On average, patients wait 2 to 10 days before seeking hospital care [9, 10, 3, 6].

Risk factors include obesity, hernia, and intense exercise [11, 1]. EA is predominant in males in the 4th or 5th decade. However, a retrospective study reported that 59% of 56 EA patients were female [11, 2, 7]. Compared to diverticulitis, left EA patients are younger and have more localized pain than diverticulitis, with diffuse pain over the left side. Despite higher BMI in left EA patients, a study of 53 patients showed no significant BMI difference between the two groups. 80% and 40% of patients had leukocytosis and fever, compared to 6% and 0% in left diverticulitis and left EA, respectively [9, 8]. In our case, the patient presented with localized left abdominal pain, consistent with most literature, and had a negative laboratory workup. However, unlike previously reported cases, our patient developed EA following blunt abdominal trauma, a mechanism not previously described in the literature to our knowledge. While trauma is not an established cause of EA, it may represent a rare contributing or confounding factor. Theoretically, blunt trauma could induce torsion or vascular injury of an epiploic appendage, triggering ischemia and thrombosis. This aligns with mechanisms described in secondary EA, where local inflammation from nearby pathology (such as pancreatitis or postoperative complications) leads to the involvement of adjacent epiploic appendages [12].

CT scan is the modality of choice with a fatty ovoid lesion surrounded by a hyperattenuating ring as the characteristic feature [2, 13, 14, 4]. A study involving 50 patients showed complete resolution of CT findings after six months [5]. Ultrasound detected EA in 7.1% of 84 patients with acute abdomen, but the diagnosis can be missed as it is limited by radiologist expertise and visceral obesity [15, 16, 17]. Our patient had the pathognomonic features of EA on a CT scan, but a follow-up scan was unnecessary.

EA is a self-limited disease typically treated with NSAIDs [2]. Surgery would be required for complications such as gangrenous EA, abscess, or obstruction [3]. A 10-year observational study found that antibiotics increased hospital stays, reducing readmissions or recurrences, though patients given opioids at discharge had fewer readmissions [7]. Symptoms are resolved within an average of 7 days [11, 14]. Recurrence of EA symptoms is extremely rare and was not reported in most literature [9, 2, 13, 3, 6, 8]. However, a retrospective study showed a 1.8% recurrence rate for EA, compared to 13% for diverticulitis patients [11].

There are no clear guidelines on EA management. Management is mentioned in case reports and case series. Diagnosing EA in acute abdomen patients is important as this can decrease hospital stays. A case series of 11 patients demonstrated that misdiagnosis of EA resulted in a prolonged average hospital stay of 4.3 days, compared to either no hospitalization or a mean stay of 1 day when correctly diagnosed. Additionally, the cost of care was significantly lower in correctly diagnosed cases ($1,205 vs. 4,117$ in misdiagnosed patients) [18].

Recent literature challenges the perception of epiploic appendagitis as a rare entity. Kahveci et al. emphasize that PEA is not truly rare but is instead underdiagnosed due to its clinical overlap with more familiar abdominal pathologies such as diverticulitis and appendicitis. Their large retrospective study of 92 patients highlights that well-localized abdominal pain with normal laboratory findings and absence of systemic symptoms should prompt consideration of PEA, especially in younger male patients. Importantly, ultrasound

was found to have 100% sensitivity and specificity in diagnosing PEA when performed at the site of maximal tenderness, supporting its use as an effective, radiation-free modality alongside CT [19].

Furthermore, a separate report by Kahveci et al. described a rare case of epiploic appendagitis of the appendix vermiformis, underscoring the diversity in the anatomical presentation of this condition. Similar to our case, their patient exhibited localized pain and normal lab results, but CT imaging was pivotal in identifying the inflamed fat-density lesion adjacent to a non-inflamed appendix. These findings reinforce the need for heightened clinical awareness and radiologic scrutiny to avoid unnecessary surgical interventions in patients presenting with atypical abdominal pain [20].

This case highlights a potentially rare association between blunt abdominal trauma and epiploic appendagitis, expanding the differential diagnosis of acute abdomen. Strengths include a clear timeline, characteristic CT findings, and complete clinical resolution with conservative management. However, as a single case, causality cannot be confirmed. The lack of baseline imaging and radiologic follow-up limits definitive conclusions, and the unique mechanism may reduce generalizability.

Given the lack of specific clinical features and the potential for EA to present without traditional risk factors, clinicians should maintain a high index of suspicion for EA in any patient with acute abdominal pain. Accurate diagnosis can prevent unnecessary interventions, reducing both healthcare costs and patient burden.

4. Conclusions

Epiploic appendagitis is a rare cause of acute abdomen that can be diagnosed with a CT scan rather than the US. Clinicians should be aware of this rare presentation to prevent unnecessary management methods as it is treated conservatively. With the increased availability and use of CT scans, the diagnosis of epiploic appendagitis is becoming more common. Further research is needed to establish standardized guidelines for its management.

Conflicts of Interest

The authors declare that they have no competing interests that could have influenced the objectivity or outcome of this article.

Funding Source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

None

Informed consent

The patient gave verbal informed consent to publish this case report and accompanying images. A standardized verbal consent documentation form was completed, witnessed, and retained by institutional protocols. All patient identifiers have been removed to protect privacy.

Large Language Model

None

Authors Contribution

All authors contributed equally to the manuscript, and all authors read and approved the final version of the manuscript.

Data Availability

All data are included in this published article.

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ASIDE Case Reports

Case Report

Rare Presentation of Werner Syndrome in a 28-Year-Old Female Patient: A Case Report and Literature Review

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ARTICLE INFO

Article history:
Received 29 May 2025
Received in revised form 21 Jun. 2025
Accepted 27 Jun. 2025
Published 1 Jul. 2025

Keywords:
Werner Syndrome
Progeria
Cataract
Leg Ulcer
Osteoporosis

ABSTRACT

Werner Syndrome (WS) is a rare autosomal recessive disorder characterized by accelerated aging and a broad spectrum of clinical manifestations. This case report presents a unique instance of WS from Pakistan, featuring a novel mutation in the WRN gene. Known as progeria adultorum, WS typically manifests post-pubertally due to mutations in the WRN gene, which plays a key role in DNA repair and genomic maintenance.

A 28-year-old woman presented with non-healing bilateral leg ulcers, dry skin, and photopsia. She exhibited multiple signs of premature aging, including short stature, early hair graying, and bilateral cataracts. Her medical history included hypothyroidism, cataract surgery, and recurrent gastrointestinal infections. Genetic testing confirmed a homozygous pathogenic variant in the WRN gene, thereby establishing the diagnosis of WS.

This case highlights the diagnostic challenges associated with rare genetic syndromes. The patient's diverse clinical signs—such as persistent ulcers, cataracts, and failure to experience a pubertal growth spurt—were consistent with diagnostic criteria for WS. The report explores the pathophysiology of WS, particularly the role of WRN mutations in impaired DNA repair and increased genomic instability, which significantly elevates cancer risk.

There is currently no specific treatment for WS; management remains supportive, focusing mainly on symptomatic relief. This case emphasizes the importance of early recognition, targeted genetic testing, and multidisciplinary care. Greater awareness and understanding of WS are essential for timely diagnosis and intervention. Furthermore, ongoing genetic research may offer valuable insights into disease mechanisms and potential therapeutic strategies, ultimately aiming to improve patient outcomes.

1. Introduction

Werner Syndrome is a rare autosomal recessive disorder characterized by accelerated aging and a constellation of clinical manifestations. Typically, it involves premature graying of hair, short stature, and joint stiffness. In this case report, we present a unique instance of Werner's syndrome (WS) originating from Pakistan, showcasing a novel mutation. WS, also known as progeria adultorum, is an autosomal recessive disorder that expedites the aging process shortly after puberty [1]. This condition emerges due to mutations within the WRN gene, which is responsible for encoding a member of the RECQ DNA helicase family, crucial for DNA repair mechanisms [2]. The hallmark features of WS encompass not only genomic instability but also the premature onset of an array of age-related ailments, such as ocular cataracts, senile appearance, diabetes mellitus, dyslipidemia, osteoporosis, arteriosclerosis, and malignancies [3, 4].

Recent insights have led to a more nuanced understanding of WS. Rather than purely accelerating aging, the absence of WRN protein appears to trigger a comprehensive decline in the regular physiological functions across diverse organs [3]. This reevaluation highlights the broader implications of the absence of WRN protein on overall health. In light of these considerations, our report examines a rare occurrence of WS, characterized by an innovative mutation originating from Pakistan.

2. Case Presentation

A 28-year-old woman presented to the medical outpatient department with persistent concerns surrounding a non-healing ulcer located on her bilateral shins and ankle region, a condition that had persisted for two months. Concurrently,

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Published in collaboration with the American Society for Inclusion, Diversity, and Equity in Healthcare (ASIDE). ISSN (Print) 3066-7224, ISSN (Online) 3066-7232 – see front matter

Citation: Muhammad Saqib, Muhammad Iftikhar, Khaqan Ahmed, Afaq Ahmed, Umar Bilal. Rare Presentation of Werner Syndrome in a 28-Year-Old Female Patient: A Case Report and Literature Review. ASIDE Case Reports. 2025;1(2):10-14, doi:10.71079/ASIDE.CR.070125126

she also experienced sensations of dry skin and persistent itching, along with occurrences of flashing lights in her eyes. The patient noted that her physical development progressed typically until the age of 10. However, subsequent to this period, her stature and weight ceased to increase, and she experienced an early onset of hair graying. No further medical workup was performed at age 10 when growth cessation was noted.

At the age of 16, she received a diagnosis of primary hypothyroidism, leading to continuous medical treatment with weight-based dosage of exogenous levothyroxine at 1 mcg per kg. Additionally, she encountered the development of cataracts in both eyes by the age of 25, necessitating surgical intervention for bilateral removal of cataracts. No further workup was done at that time. The patient disclosed a history marked by recurrent gastrointestinal infections (leading to symptoms of watery diarrhea for 2 weeks) every 1 or 2 months, and a decade following her entry into puberty at age 17, she noted a gradual thinning of her voice. She was empirically treated for the gastrointestinal infections with metronidazole and supportive management, and no further workup was done to identify the specific organisms. She remained unmarried and without any offspring.

Approximately four months prior to her presentation, she encountered an itchy rash on her lower leg and ankle. Persistent scratching led to the formation of an ulcer in the affected region. A thorough clinical assessment unveiled several distinctive features, including a prematurely aged appearance, limited height, parched skin, diminished hair volume, taut skin accompanied by subcutaneous atrophy, and lips displaying pursed contours with furrowing, as shown in **(Figure 1)**.

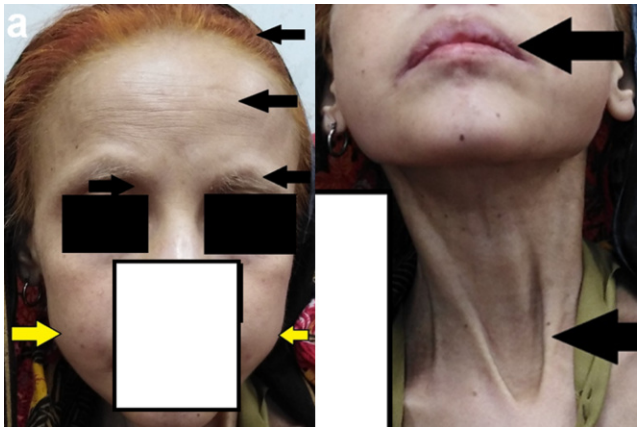

Figure 1: (a) Upper arrows (black) pointing to graying and blonding of hair and eyebrows, while the lower arrows (yellow) point to the maxillary hyperplasia seen in our patient. (b) Upper black arrow (black) pointing towards cracked lips and lower arrow (black) pointing to the significant wasting seen in our patient.

Further physical examination revealed well-defined tender ulcers, characterized by hyperkeratotic borders, situated over the region encompassing the bilateral lower legs, as shown in **(Figure 2)**. The ulcer's floor exhibited pale granulation tissue along with a clear discharge, while the surrounding skin displayed signs of erythema indicative of eczematous changes. Notably, significant limb wasting was also observed.

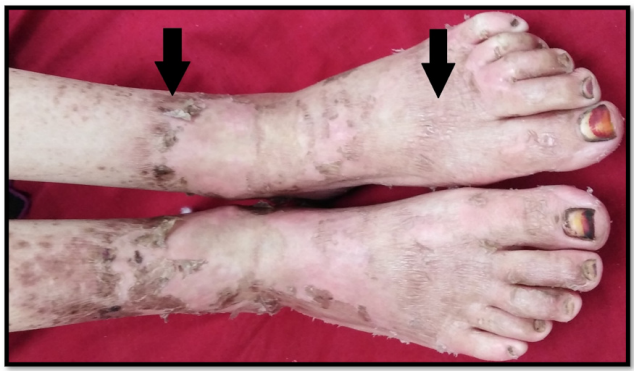

Figure 2: Extensive scaling and desquamation after ulcer resolution on bilateral legs, ankles, and feet region, seen in our patients.

Routine investigations, including hormone assessments, yielded results within typical ranges. However, the patient's thyroid-stimulating hormone levels were elevated (34 mIU/L), suggesting uncontrolled hypothyroidism (since her 1 mcg per kg dose was way below the recommended dosage of 1.6 mcg per kg), which was then subsequently corrected to the recommended dose. A biopsy of the ulcer was conducted, yielding no indications of dysplasia or malignancy. Radiographic evaluation of the foot disclosed indications of osteoporosis as shown in **(Figure 3)**.

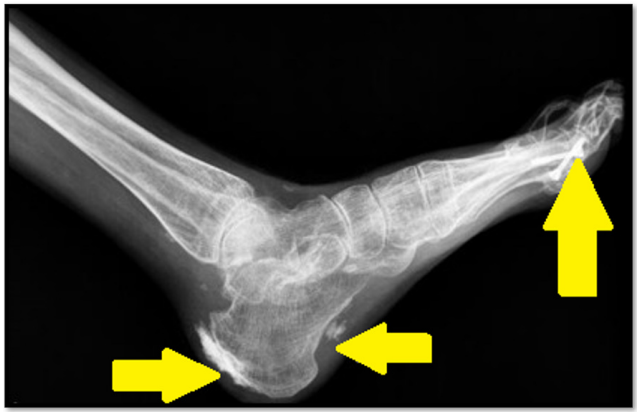

Figure 3: Lateral foot x-ray showing evidence of osteosclerosis in the proximal interphalangeal joint (yellow right-sided arrow); soft tissue calcification at the posterior calcaneal region (yellow right-sided arrow) and osteoporotic lesions at the inferior calcaneal regions (yellow left-sided arrow) seen in our patient.

Conducting genetic analysis in accordance with the International Registry of Werner Syndrome revealed a substitution mutation characterized by a homozygous pathogenic variant c.3190 C>T in exon 26 of the WRN gene [5, 6]. This finding was subsequently verified through Sanger sequencing. The patient received comprehensive counseling regarding her condition and its potential long-term ramifications. She

currently remains under regular surveillance to enable the early detection of cutaneous malignancies and cardiovascular complications. Follow-up a month after the change in levothyroxine dosage revealed a trend towards lowering of the TSH to 15 mIU/L along with improvement of the hypothyroidism symptoms, suggesting that a therapeutic dose was being delivered to the patient.

3. Discussion

This case serves as a quintessential illustration of the intricate diagnostic journey required to uncover rare genetic disorders. The initial presentation of left leg ulcers, fever, and joint pain was enigmatic, necessitating a sequential exclusion of common causes.

When evaluating a patient with suspected Werner Syndrome (WS), several differential diagnoses must be considered due to overlapping clinical features. Hutchinson-Gilford Progeria Syndrome (HGPS) is a notable progeroid disorder that presents in early childhood with growth retardation and cardiovascular complications. Still, it lacks cataracts and typically has an earlier onset than WS [7]. Rothmund-Thomson Syndrome (RTS) may resemble WS due to features like cataracts and increased cancer risk; however, its hallmark findings include poikiloderma and skeletal anomalies [8]. Cockayne Syndrome also presents with growth failure and premature aging, but is distinguished by early-onset neurodevelopmental delay and photosensitivity [9]. Bloom Syndrome is characterized by short stature, photosensitive rash, and chromosomal instability, yet lacks the accelerated aging and ocular involvement seen in WS [10]. Systemic sclerosis can mimic WS with features such as skin tightening and chronic ulcers, but it is an autoimmune condition that is identifiable by serologic markers and internal organ involvement [11]. Mandibuloacral dysplasia, a laminopathy, shares traits such as lipodystrophy and skeletal abnormalities, but is differentiated by its distinctive craniofacial and metabolic features [12]. Careful clinical evaluation and genetic testing are crucial for distinguishing WS from these overlapping syndromes. Genetic testing, ultimately revealing mutations in the WRN gene, unveiled the rare genetic etiology. Radiographic findings further aligned with the clinical presentation, underscoring the complexity and diversity of Werner Syndrome's manifestations.

Werner's syndrome (WS) is a genetic disorder inherited in an autosomal recessive manner, first elucidated by Otto Werner, a German physician, in 1904. His initial account detailed four instances of siblings displaying symptoms like juvenile cataracts, scleroderma-like alterations in their extremities, stunted growth, premature aging of facial features, graying hair, and hypogonadism [13, 14]. Cases of WS have emerged across various populations, with a particularly pronounced prevalence observed in Japan (with an estimated occurrence of 1 in 100,000) and the Sardinia province of Italy [15, 16]. A salient initial sign often noticed is the absence of the anticipated growth spurt during puberty, a phenomenon evident in our case. An almost ubiquitous observation in WS is the presence of bilateral cataracts

Table 1: Application of the diagnostic criteria of the International Registry of Werner Syndrome in our patient.

Cardinal Signs and Symptoms	Present Case
Cataract (bilateral)	Present
Short stature	Present
Characteristic dermatological pathology	Present
Parental consanguinity	Present
Premature graying and/or thinning of scalp hair	Present
Diabetes mellitus	Absent
Hypogonadism	Present
Osteosclerosis of the distal phalanges of the digits	Present
Osteoporosis	Present
Soft tissue calcification	Present
Voice changes	Present
Flat feet	Present
Evidence of premature atherosclerosis	Absent
Any mesenchymal/rare/multiple neoplasms	Absent

in conjunction with non-healing ulcers affecting the lower legs region. Other clinical attributes include skin atrophy, a pinched facial appearance, thin and gray hair, a hoarse voice, diabetes, atherosclerosis, skin ulcers, hypogonadism, and osteoporosis. Malignancy and myocardial infarction emerge as the most prevalent causes of death in the fifth decade of life [3]. Among WS patients, the most commonly reported malignancies comprise thyroid carcinomas (16%), followed by melanoma, soft tissue sarcomas, and leukemia [17]. Our patient's diagnosis of WS aligns with the diagnostic criteria laid out by the International Registry of Werner Syndrome (IRWS) as presented in **(Table 1)** [18].

The presence of homozygous or compound heterozygous loss-of-function mutations in the WRN gene underpins Classic WS. WRN localizes within the nucleolus, translocating to the site of DNA strand breaks. Evidence suggests that WRN engages in various cellular processes, including DNA replication, recombination, and repair, telomere maintenance, transcription, mitochondrial function, and epigenetic alterations. In a proliferating cell, the WRN protein displays affinity for specific substrates like G4 quadruplexes, holiday junctions, and bubble structures, facilitating its role in DNA repair [18]. To date, approximately 86 distinct WRN mutations have been documented. These have been succinctly reviewed by Yokote et al. and other sources [19, 6]. Most of these mutations involve stop codons, which can potentially result in the loss of nuclear localization of the WRN protein. Consequently, the mutated WRN protein fails to access the nucleus [20]. The WRN gene promotes genomic stability and DNA repair, rendering WS patients predisposed to various forms of cancer. Notably, C-terminal WRN mutations have been closely linked to follicular thyroid carcinoma [21].

Regrettably, no specific treatments targeting WS are presently available. Nonetheless, ongoing research explores novel therapeutic avenues, including p38 mitogen-activated protein kinase inhibitors with implications for aging and age-related ailments [22]. Managing WS typically involves

symptomatic treatments tailored to individual organ involvement, whereas addressing non-healing cutaneous ulcers requires a proactive approach.

4. Conclusion

This case report sheds light on the intricate clinical phenotype and genetic basis of Werner syndrome (WS), highlighting the diverse range of symptoms that encompass premature aging, cataracts, skin atrophy, and non-healing ulcers. The discovery of a novel homozygous pathogenic variant within the WRN gene underscores the genetic heterogeneity of WS. Unilateral chronic ulcers in the lower legs, along with vision abnormalities, should awaken a clinician to the possibility of this syndrome as one of the differential diagnoses. The case underscores the need for heightened awareness, early diagnosis, and comprehensive management strategies for WS patients, while also highlighting the ongoing significance of genetic research to deepen our understanding of this complex disorder and potentially inform future therapeutic avenues.

Conflicts of Interest

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

Funding Source

No funding was received for this article.

Acknowledgments

None

Informed consent

Before inclusion in the study, written informed consent was obtained from the patient.

Large Language Model

No large language models (LLMs) were used in manuscript preparation.

Authors Contribution

MS contributed to conceptualization, methodology, data collection, software, original manuscript drafting, and visualization; MI contributed to conceptualization, methodology, data collection, data curation, writing the original manuscript draft, and validation; KA contributed to conceptualization, data collection, data analysis and interpretation, and writing—reviewing and editing; AA and UB contributed to supervision, funding acquisition, project administration, manuscript review, and editing.

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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Case Report

A Hidden Cause of Bone Fragility: Late Diagnosis of Hypophosphatasia in a 40-Year-Old Female

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ARTICLE INFO

Article history:
Received 5 Mar. 2025
Received in revised form 21 Jun. 2025
Accepted 29 Jun. 2025
Published 4 Jul. 2025

Keywords:
Hypophosphatasia
Alkaline Phosphatase
ALPL Gene
Asfotase Alfa
Metabolic Bone Disease

ABSTRACT

Hypophosphatasia (HPP) is a rare inherited metabolic disorder caused by loss-of-function mutations in the ALPL gene, leading to deficient activity of tissue-nonspecific alkaline phosphatase (TNSALP). This results in impaired bone and dental mineralization, causing a wide range of clinical manifestations, from perinatal lethality to mild adult-onset forms. We report a case of a 40-year-old female with a history of joint pain, multiple fractures, dental issues, and bipolar disorder, who was diagnosed with adult-onset HPP. Laboratory investigations revealed persistently low alkaline phosphatase (ALP) levels and elevated vitamin B6. Genetic testing confirmed a pathogenic ALPL mutation. The patient was initiated on enzyme replacement therapy (ERT) with asfotase alfa, resulting in significant symptom improvement. This case highlights the importance of recognizing HPP in adults with unexplained musculoskeletal symptoms and underscores the role of genetic testing in the diagnosis and management of this condition.

1. Introduction

Hypophosphatasia (HPP) is a rare, inherited metabolic disorder that primarily affects the bones and teeth, as well as other systemic manifestations. It results from loss-of-function mutations in the ALPL gene, which encodes the tissue-nonspecific alkaline phosphatase (TNSALP) enzyme [1]. This gene, comprising 12 exons, encodes the TNSALP protein, which is expressed in various tissues, including bone, liver, and kidney [2]. TNSALP hydrolyzes inorganic phosphates, and its deficient activity in the case of HPP leads to the accumulation of its substrates, mainly Pyridoxal-5′-phosphate (PLP), inorganic pyrophosphate (PPi), and phosphoethanolamine (PEA) [3]. Defective PLP metabolism can result in seizures, whereas excessive PPi hinders bone mineralization. The effects of PEA buildup remain largely unexplored [4].

HPP was first described in 1948 by J.C. Rathbun; its genetic basis wasn't identified until 1988 by Harry Harris and the team [5, 6]. Since then, more than 300 mutations in the ALPL gene have been documented [7], causing an extremely variable clinical spectrum ranging from the very severe, mostly lethal, perinatal form to a mild form with late adult onset presenting with non-pathognomonic symptoms such as arthropathy and musculoskeletal pain [8].

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Published in collaboration with the American Society for Inclusion, Diversity, and Equity in Healthcare (ASIDE). ISSN (Print) 3066-7224, ISSN (Online) 3066-7232 –

Citation: Mohamed M, Keshk M, Hassan A, Hassan AH, Kela G. A Hidden Cause of Bone Fragility: Late Diagnosis of Hypophosphatasia in a 40-Year-Old Female. ASIDE Case Reports. 2025;1(2):15-18, doi:10.71079/ASIDE.CR.07042548

The primary clinical features stem from impaired bone and tooth mineralization, leading to rickets, osteomalacia, fractures, and tooth loss. However, in severe cases, additional systemic complications such as seizures, respiratory and renal issues, chronic pain, and muscle weakness may also occur [9]. These systemic effects could be linked to TNSALP's involvement in purinergic signaling through ATP dephosphorylation, a process crucial for the central nervous system, bones, and other organs [10, 11].

The diagnosis of HPP is confirmed through clinical symptoms, imaging studies, and laboratory evaluations. Key laboratory findings supporting the diagnosis include reduced serum alkaline phosphatase (ALP) activity adjusted for age and sex, along with elevated plasma vitamin B6 and urinary PEA levels [12]. However, due to the clinical overlap of HPP with more common conditions like osteoporosis or osteomalacia, many affected individuals are likely to remain undiagnosed or be misdiagnosed with other disorders [13]. We report a case of HHP confirmed through genetic testing in a 40-year-old female with a history of bipolar disorder, presenting with joint pain and low alkaline phosphatase levels, who was referred for further evaluation. This case highlights the importance of recognizing hypophosphatasia in patients with chronic symptoms and biochemical findings suggestive of the condition.

2. Case Presentation

A 40-year-old female occupational therapist presented with a 15-year history of progressively worsening joint pain. Initially, the pain predominantly affected her hands, fingers, and toes, and after 10 years, she developed intermittent knee pain. Over time, she experienced multiple fractures, including a leg fracture after a fall, an arm fracture, and several toe fractures from regular activities.

Table 1: Laboratory Test Results

Laboratory Test	Patient Result	Reference Value
ALP	20–40 U/L	44–147 U/L
Vitamin B-6	157.2 mcg/L	5–50 mcg/L
Calcium	9.1 mg/dL	8.5–10 mg/dL
Phosphorus	3.9 mg/dL	2.5–4.5 mg/dL
25-OH Vitamin D	54.1 ng/mL	20–50 ng/mL
Bone-specific ALP	860 U/L	6.5–20.1 U/L

ALP, Alkaline Phosphatase;

Additional clinical features included dental caries with cavities, jaw pain, and difficulties with chewing. Her past medical history was notable for bipolar II disorder with depressive symptoms and anxiety, managed with carbamazepine and venlafaxine, as well as asthma. The patient's family history is significant for her mother having experienced a vertebral fracture and metastatic renal cancer, while both of her children have a history of metatarsal fractures. This complex clinical presentation, along with progressive skeletal issues and dental abnormalities, warranted further investigation. The patient's previous rheumatology evaluations identified early signs of non-arthritis-related joint issues and mild Raynaud's phenomenon. On physical examination, her vital signs, including blood pressure, heart rate, respiratory rate, and temperature, were within normal limits. Her BMI was 30.04 kg/m², indicating obesity. Physical examination findings were notable for discomfort during fist-making and joint palpation, with no other significant abnormalities. Laboratory investigations revealed persistently low ALP levels since the age of 34, ranging from 20 to 40 U/L (reference range: 44–147 U/L), alongside elevated vitamin B6 levels at 157.2 mcg/L (reference range: 5–50 mcg/L). Her bone mineral density (BMD) was low. Notably, her 25-OH vitamin D levels were elevated at 54.1 ng/mL (reference range: 20–50 ng/mL), and bone-specific ALP was markedly elevated at 860 U/L (reference range: 6.5 to 20.1 U/L). Calcium and phosphorus levels were within normal limits at 9.1 mg/dL and 3.9 mg/dL, respectively. Despite a prolonged 15-year diagnostic challenge, genetic analysis revealed a pathogenic mutation in the ALPL gene, confirming a diagnosis of hypophosphatasia associated with this pathogenic variant. Management included calcium supplementation and injury prevention strategies. The patient was initiated on Strensiq (asfotase alfa) injections at a dose of 2 mg/kg (125 mg) three times per week, which she continued for one year. The treatment was well-tolerated, with only localized soreness and burning at injection sites as side effects, which were manageable. Adherence to the treatment plan resulted in stabilization of BMD and significant improvement in joint symptoms. The patient reported an improved functional status and a reduction in jaw pain. Additionally, her ALP levels stabilized, and no new fractures were reported.

3. Discussion

HPP is a rare genetic disorder linked to mutations in the ALPL gene, which encodes the TNSALP enzyme, crucial for bone and dental mineralization [14] . The molecular mechanisms underlying HPP are complex. TNSALP is an enzyme found on the surface of cells in the bone, kidney, and liver [6]. When ALP activity is deficient, its substrates— inorganic PPi and PLP—can accumulate outside cells [15] The buildup of PPi can interfere with the mineralization of bones and teeth and contribute to pseudogout [15, 4]. Additionally, reduced hydrolysis of PLP can lead to vitamin B6 deficiency in the central nervous system and a decrease in neurotransmitter production, potentially resulting in pyridoxine-responsive seizures in severely affected infants [16, 4]. PEA, another substrate of TNSALP and a biochemical marker for HPP, is elevated in patients with this condition, although its physiological significance remains unclear. PEA levels can be measured through plasma or urine amino acid testing [4].

In this case of the 40-year-old female patient, the combination of her psychiatric symptoms, including bipolar disorder and depression, alongside musculoskeletal complaints like hand and toe joint pain, knee pain, jaw pain, and difficulty chewing, suggested a possible systemic issue. The patient's elevated vitamin B6 levels and consistently elevated ALP levels were red flags that led clinicians to suspect HPP.

The clinical picture of this patient was further complicated by a history of multiple fractures, including childhood leg fractures and recent toe fractures, which are characteristic of the brittle bones often seen in HPP [17]. However, her hand X-ray appeared normal, suggesting that significant bone mineralization defects were not yet visible, though her significant dental issues, such as cavities and difficulty chewing, further supported the presence of mineralization defects. Additionally, the patient's family history is significant for her mother having experienced a vertebral fracture and metastatic renal cancer. Notably, both of her children have a history of metatarsal fractures, which may be clinically relevant in the context of the patient's confirmed ALPL mutation. Given the autosomal dominant inheritance pattern of many adult-onset hypophosphatasia cases, the absence of formal genetic counseling and family screening represents a critical oversight. Early identification of affected family members, particularly in children with signs suggestive of skeletal fragility, is essential for proactive management. Genetic counseling should be offered to the patient and her family to explain inheritance risks, discuss the utility of biochemical screening (e.g., ALP and vitamin B6 levels), and consider genetic testing for at-risk relatives. A structured approach to evaluating her children—starting with a thorough musculoskeletal and dental history, followed by targeted laboratory assessments and genetic confirmation if indicated—can facilitate timely diagnosis and early intervention, thereby minimizing potential complications and improving long-term outcomes.

A key aspect of HPP diagnosis is the measurement of serum ALP levels but by itself is not sufficient for a diagnosis as this is complicated by the fact that other several conditions unrelated to bone can also present with low ALP, such as celiac disease, severe anemia, hypothyroidism, Wilson's disease, malnutrition, massive transfusion of blood or plasma, early pregnancy, and drugs [18, 19]. It has also been reported in severe osteogenesis imperfecta [20], cleidocranial dysplasia [21], and osteochondrodysplasia [22]. It's also worth noting that serum ALP levels do significantly vary with age and sex.

Measuring serum ALP level is an affordable and reasonable parameter for HPP. However, to reach a definitive diagnosis in this case, genetic testing played a crucial role. Genetic testing revealed a heterozygous mutation in the ALPL gene (c.980T>G, p.Phe327Cys), which is associated with low serum ALP levels and low bone mineral density, confirming the diagnosis of adult-onset HPP. This mutation, although less severe than homozygous mutations [23], was consistent with the patient's clinical presentation of joint pain, fractures, and dental issues.

This case also highlights the importance of bone-specific ALP measurements and the testing of TNSALP substrates, such as PLP and PEA, as they can provide more accurate insights into the patient's condition. Although total ALP levels may appear normal in some cases, as reported by Dattagupta [24], the bone-specific ALP test can help detect TNSALP deficiency, along with elevated PLP and PEA. Additionally, radiological findings such as osteopenia, pseudofractures, and calcific periarthritis, although not observed in this patient's X-ray, are commonly seen in individuals with HPP [25].

Despite the challenges in diagnosing HPP in adults, the patient's diagnosis prompted an adjustment to her treatment plan. Although there is no definitive treatment for adult-onset HPP [26], enzyme replacement therapy (ERT) with Strensiq (asfotase alfa) has been shown to improve bone mineralization, reduce fractures, and alleviate musculoskeletal pain in pediatric patients with HPP [27]. Although Strensiq is not officially approved for adult-onset HPP [27], the patient began treatment and reported significant improvements in her symptoms after one year, including better bone health, reduced pain, and improved dental health. This illustrates that even in cases of retroactive diagnosis in adults, ERT can provide substantial benefits, significantly improving quality of life and potentially enabling patients to continue their careers and daily activities.

This case report is limited by its single-patient design, which restricts generalizability and precludes causal conclusions. Retrospective data collection introduces potential recall bias, and some aspects of the patient's medical and psychosocial history were not fully documented. The short follow-up period limits evaluation of long-term treatment outcomes. Outcome assessment relied on subjective reports without objective functional measures, and the absence of a control group prevents comparison with natural disease progression or alternative management strategies.

4. Conclusion

This case report highlights the importance of recognizing HPP in adults presenting with unexplained musculoskeletal pain, multiple fractures, and dental abnormalities. The patient faced a prolonged diagnostic delay despite persistent ALP levels and characteristic clinical features. Genetic testing ultimately confirmed the diagnosis, emphasizing its crucial role in definitive diagnosis when biochemical markers alone are inconclusive.

The initiation of ERT with asfotase alfa (Strensiq) led to marked clinical improvements. This underscores the potential benefits of ERT in adult-onset HPP, despite its primary approval for pediatric patients. This case reinforces the need for early recognition and comprehensive evaluation of HPP in adults. Increased awareness among clinicians can prevent misdiagnosis, allowing timely intervention and improved patient outcomes. Further research is warranted to optimize treatment strategies for adult-onset HPP and assess the long-term benefits of ERT in this population. Patient

Conflicts of Interest

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

Funding Source

No funding was received for this article.

Acknowledgments

None

Informed consent

Patient consent was obtained from the patient.

Large Language Model

No large language models were used in manuscript preparation.

Authors Contribution

All authors have participated in data collection, writing the manuscript, and revising the final manuscript

Data Availability

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

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ASIDE Case Reports

Case Report

Rare Case of Disseminated Nocardiosis with Simultaneous Lung, Brain, and Spinal Cord Involvement in a Patient with Sarcoidosis

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ARTICLE INFO

Article history:
Received 12 Jan. 2025
Received in revised form 10 Apr. 2025
Accepted 6 May 2025
Published 29 Jul. 2025

Keywords:
Nocardia
Nocardiosis
Sarcoidosis
Case report

ABSTRACT

Nocardiosis is an uncommon opportunistic infection commonly affecting the lungs in immunocompromised individuals. We present an unusual case of disseminated nocardiosis involving the spinal cord and brain in a patient previously diagnosed with sarcoidosis and treated with glucocorticoids. We are presenting the case of a 46-year-old Caucasian male with sarcoidosis who develops pulmonary nocardiosis, with chest X-ray (CXR) revealing left lower lobe infiltrates diagnosed as community-acquired pneumonia usually caused by Nocardia, confirmed by excisional biopsy. A few days later, the disease progressed to the spinal cord, leading to an epidural abscess, and disseminated to the brain, leading to multiple ring-enhancing lesions confirmed by MR. Timely surgical intervention, such as abscess drainage, is crucial in the management of abscesses to prevent life-threatening complications and preserve neurological function. Clinicians should maintain a broad differential diagnosis when evaluating new pulmonary infiltrates in patients with sarcoidosis. Early CNS imaging should be considered in cases of severe pulmonary nocardiosis to prevent catastrophic complications.

1. Introduction

Nocardiosis is a rare opportunistic infection caused by aerobic, gram-positive bacteria with a filamentous and branched appearance, partially acid-alcohol resistant, belonging to the genus Nocardia [1]. It affects approximately 500–1000 individuals annually in the United States, according to the Centers for Disease Control and Prevention [2]. Nocardiosis manifests in localized or disseminated forms, with pulmonary nocardiosis being the most common presentation. This typically includes pneumonia, lung abscesses, endobronchial masses, or cavitary lesions [3]. Disseminated nocardiosis, particularly central nervous system (CNS) involvement, represents a life-threatening associated with high mortality and relapse rates, especially among immuno-compromised individuals [4]. Although Nocardia can infect both immunocompetent and immunocompromised individuals, the disseminated disease is more common in immunocompromised individuals, particularly in sarcoidosis patients on long-term corticosteroid therapy. While corticosteroids are effective in managing sarcoidosis symptoms, their prolonged use leads to side effects such as weight gain, insulin resistance, and increased susceptibility to infections. This report highlights a unique case of pulmonary nocardiosis in a sarcoidosis patient, with no prior cases documented simultaneous lung, brain, and spinal cord involvement in such patients. The report aims to concisely review this rare and challenging condition's clinical, pathogenetic, and diagnostic features.

2. Case Presentation

A 46-year-old Caucasian male with a significant past medical history of chronic obstructive pulmonary disease (COPD), gastroesophageal reflux disease (GERD), hypothyroidism, and sarcoidosis presented to the emergency department with a three-day history of cough and fever. His current medications included Advair, Proventil, prednisone (50 mg daily for two months), Synthroid, Nasacort, and Prilosec.

2.1. Initial Presentation and Evaluation

On admission, vital signs were notable for a body temperature of 99.6°F, a pulse rate of 68 beats per minute, respiratory rate of 18 breaths per minute, and blood pressure of 128/76 mmHg. Laboratory findings were as follows: White Blood Cell Count (WBC): 27,300 cells/mm³ (84]% granulocytes, 4% lymphocytes), Electrolytes: Sodium 140 mmol/L, Potassium 4.7 mmol/L, Chloride 99 mmol/L, Bicarbonate 30 mmol/L, Renal Function: Blood Urea Nitrogen (BUN) 21 mg/dL, Creatinine 1.0 mg/dL, Blood Glucose: 104 mg/dL. A chest X-ray (CXR) demonstrated infiltrates in the left lower lobe.

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Published by the American Society for Inclusion, Diversity, and Equity in Healthcare (ASIDE). ISSN (Print) 3066-7224, ISSN (Online) 3066-7232 – see front matter

Citation: Elazab A, Nazmy A, Ahmed N, Hassan A, Marte E. Rare Case of Disseminated Nocardiosis with Simultaneous Lung, Brain, and Spinal Cord Involvement in a Patient with Sarcoidosis. ASIDE Case Reports. 2025;1(2):19-21, doi:10.71079/ASIDE.CR.07292524

2.2. Initial Management

The patient was empirically treated for community-acquired pneumonia with intravenous ceftriaxone and azithromycin. Blood, sputum, and urine cultures were obtained but were negative for microbial growth. The patient was discharged with oral cefpodoxime and azithromycin.

2.3. Readmission (Day 6)

On the sixth day following discharge, the patient returned with worsening symptoms, including increased cough, sputum production, shortness of breath, and left-sided chest pain. Imaging studies revealed the progression of left lower lobe consolidation. Further investigations, including an excisional biopsy, confirmed a diagnosis of nocardiosis. The patient was discharged with oral trimethoprim-sulfamethoxazole (Bactrim).

2.4. Second Readmission (Day 13)

On the thirteenth day after initial discharge, the patient presented with severe back pain, paraparesis, and urinary retention. Magnetic Resonance Imaging (MRI) of the spine identified an epidural abscess at the T4-T5 levels. MRI of the brain further revealed multiple ring-enhancing lesions consistent with brain abscesses. A surgical procedure was performed to drain the brain abscess.

2.5. Outcome and Follow-Up

Following the surgical intervention, the patient was discharged to a rehabilitation facility to continue care with intravenous antibiotic therapy targeting nocardiosis.

3. Discussion

Nocardia spp are gram-positive bacilli that form branching hyphae, non-spore-forming, and weakly acid-fast bacteria. Nocardia is a rare opportunistic infection that occurs mainly in patients with low immunity, such as chronic corticosteroid users, organ transplant recipients, and HIV/AIDS patients; however, it may also occur in immunocompetent patients. Infection with Nocardia can occur due to inhalation, which is the most common route, presenting with pneumonia, lung abscess, and cavitary lesions) or through direct inoculation of the skin, which causes cutaneous nocardiosis-cellulitis and ulcers, alongside the infection may then spread to the bones, joints, heart, kidneys, brain, and eyes [3]. Disseminated Nocardia is a life-threatening condition that mainly occurs in severely immunocompromised patients with a mortality rate of up to 85%. It begins as pulmonary Nocardiosis, then involves other organs, which, like our patient, starts as left pneumonia and then disseminates to the brain as multiple abscesses and the spinal cord as an epidural abscess at T4-T5 [5]. A few case reports describe sarcoidosis with disseminated nocardiosis on long-term corticosteroids [6, 7, 8, 9, 10, 11, 12]. Our patient is unique as no cases have documented simultaneous involvement of the lungs, brain, and spinal cord in such patients. Patients who have underlying structural lung illness are more likely to develop pulmonary nocardiosis [13]. Our patient, reported in this case, has a history of sarcoidosis, which probably contributed to him being more vulnerable to primary pulmonary nocardiosis. He was also immunocompromised on chronic prednisone therapy, which rendered him more susceptible to the illness spreading to his brain and spinal cord through the bloodstream. Our patient presented nonspecific symptoms such as cough and fever, which occur with other respiratory organisms. This led to the initial diagnosis of community-acquired pneumonia without suspicion of pulmonary nocardiosis. The clinical manifestations of a Nocardia spp. Pulmonary infections are similar to those of pulmonary tuberculosis (fever, cough, chest pain, night sweats, weight loss, and pneumonia); therefore, the nonspecific feature of the clinical symptoms, as well as the challenge of isolating the organisms in the laboratory, lead to delayed of diagnosis of nocardiosis [3]. Early diagnosis and treatment are essential in patients with nocardiosis. Diagnosis typically requires the organisms to be detectable in smears or sections examined under a microscope, and their isolation and identification are done through microbiologic culture. Sputum smear results are frequently negative. Nocardia species are identified using a modified acid-fast stain containing 1% sulfuric acid, where the bacilli appear as pink filament branching hyphae [3, 5]. Mass spectrometry and other modern molecular biology technologies, especially PCR and 16S rDNA sequencing, could accurately and rapidly identify Nocardia species [3]. In our case, the blood, sputum, and urine cultures were negative when present on admission. On the 6 days of discharge, the patient's symptoms increased and presented with worsening cough, sputum production, shortness of breath, and left-sided chest pain, which led us to do an excisional biopsy to confirm the diagnosis and proper management of the patient. On the 13 days of discharge, the patient presented with severe back pain, paraparesis, and urinary retention, which demonstrated the significance of doing a brain MRI on every patient diagnosed with nocardiosis as most of the patients with CNS nocardiosis had no neurological symptoms [11]. The severity of this case highlights that they need prophylaxis against nocardiosis. Some studies suggest prescribing Trimethoprim-sulfamethoxazole as prophylaxis in patients with immunocompromised [14]. The patient, in this case, was receiving prednisone (50 mg daily for two months, which made him need prophylaxis. For the treatment of nocardiosis, trimethoprim/sulfamethoxazole (TMP/SMX) is the drug of choice [15]. However, the Treatment of Nocardia should be guided by Nocardia speciation and susceptibility testing. Non-severe pulmonary nocardiosis and cutaneous infections can be treated with TMP/SMX monotherapy. In the case of sulfa allergy or resistance, another drug like amikacin, imipenem, meropenem, ceftriaxone, cefotaxime, minocycline, moxifloxacin, levofloxacin, linezolid, tigecycline, and amoxicillin-clavulanic acid can be used. The choice of alternative antibiotics should be guided by in vitro susceptibility data in case of immunocompromised patients or those with disseminated disease or CNS involvement; it is recommended that TMP/SMX be administered together with meropenem, imipenem or amikacin. Initial combination therapy is better than TMP/SMX alone as it showed that antibiotic susceptibility patterns of Nocardia spp isolated from the United States of America revealed that more than 50% of isolates were resistant to TMP/SMX. Duration of therapy depends on the patient's immune state and the lesion's location; it is recommended for at least 4 to 6 months in pulmonary nocardiosis, 3M in a skin lesion, and 12m in CNS involvement [3, 15, 16]. Our case was first treated with ceftriaxone and azithromycin when cough and fever were present. After confirmation of diagnosis with Nocardia, the treatment was changed to TMP/SMX. However, the Nocardia disseminates to the brain and spinal cord; the treatment changed to IV antibiotic therapy. This case underscores the importance of considering Nocardia infection in immunocompromised patients and those with pre-existing structural lung disease. Brain imaging should be performed in suspected or confirmed nocardiosis cases, as many patients with CNS involvement lack neurological symptoms. Prompt diagnosis and treatment are crucial to avoid severe complications.

4. Conclusions

This is the first reported case of Nocardia affecting the lungs, brain, and spinal cord simultaneously. Clinicians should maintain a broad

differential diagnosis when assessing new pulmonary infiltrates in sarcoidosis patients. Additionally, early CNS imaging is advisable in severe pulmonary nocardiosis to prevent devastating outcomes.

Conflicts of Interest

The authors declare that they have no competing interests that could have influenced the objectivity or outcome of this investigation.

Funding Source

No funding was received for this article.

Acknowledgments

None

Informed consent

Verbal consent was obtained from the patient and family to publish this case report. All relevant information and confidentiality rights were explained, and identifying details have been anonymized.

Large Language Model

None

Authors Contribution

All authors contributed equally to this work.

Data Availability

All the data is available with the corresponding Author upon request.

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