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Bapoma Breathlessness Syndrome and Type 2 Eosinophilic Airway Involvement: A Case Study

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Abstract

BAP1 tumour predisposition syndrome (BAP1-TPDS) is a rare autosomal dominant cancer susceptibility syndrome associated with multiple malignancies, including mesothelioma and melanoma. Respiratory symptoms in affected patients may therefore raise concern for thoracic malignancy, although alternative treatable causes should be considered. A 17-year-old female with a pathogenic germline BAP1 variant presented with a four-year history of exertional breathlessness despite treatment for asthma. Chest radiography and high-resolution CT were normal. Pulmonary function testing demonstrated preserved spirometry with mild air trapping, while prominent glottic closure during testing raised suspicion for inducible laryngeal obstruction (ILO). Fractional exhaled nitric oxide was markedly elevated (67.5 ppb), with significant house dust mite sensitisation and elevated total IgE, supporting coexisting Type 2-high allergic asthma. Treatment was escalated to ICS/LABA/LAMA therapy, together with allergen avoidance, speech pathology assessment for ILO, and breathing retraining. This case highlights the coexistence of allergic eosinophilic asthma and probable ILO in a patient with BAP1-TPDS. Respiratory symptoms in this population should not automatically be attributed to BAP1-associated malignancy. FeNO, comprehensive pulmonary function testing, and assessment for ILO can help identify treatable alternative causes of breathlessness.

Keywords: BAP-1 tumour predisposition syndrome; Eosinophilic asthma; Inducible laryngeal obstruction; Vocal cord dysfunction; House dust mite allergy; Breathlessness; Type 2 inflammation; Fractional exhaled nitric oxide

Introduction

The BRCA1-associated protein-1 (BAP1) gene, located on chromosome 3p21.1, encodes a ubiquitin carboxy-terminal hydrolase that functions as a tumour suppressor protein involved in the regulation of cell proliferation, DNA damage response, and cell death pathways [1]. Germline mutations in BAP1 are associated with the BAP-1 tumour predisposition syndrome (BAP1-TPDS), an autosomal dominant condition characterized by an increased lifetime risk of multiple malignancies including uveal melanoma, cutaneous melanoma, renal cell carcinoma, mesothelioma, and other neoplasms [2,3]. The syndrome exhibits high penetrance, with individuals carrying a pathogenic BAP1 variant having a significant lifetime risk of developing these tumours [4]. Respiratory manifestations of BAP1-TPDS are predominantly neoplastic, with mesothelioma being the most commonly reported pulmonary malignancy in affected individuals [5]. However, patients with BAP1-TPDS may present with respiratory symptoms that are unrelated to their genetic predisposition, necessitating thorough diagnostic evaluation to exclude both BAP-1-associated malignancies and alternative pulmonary pathologies. Asthma is a chronic inflammatory airway disease characterized by variable airflow obstruction, bronchial hyperresponsiveness, and respiratory symptoms including wheeze, breathlessness, chest tightness, and cough [6]. Type 2 (T2) eosinophilic asthma is a specific phenotype driven by T-helper 2 cell-mediated inflammation, characterized by elevated levels of fractional exhaled nitric oxide (FeNO), peripheral eosinophilia, and elevated immunoglobulin E (IgE) [7]. This

phenotype typically responds well to inhaled corticosteroids and biologic therapies targeting Type 2 inflammatory pathways [8].

Fractional exhaled nitric oxide (FeNO) has emerged as a valuable, non-invasive biomarker of airway inflammation in asthma management [9]. Nitric oxide is produced by airway epithelial cells via the inducible nitric oxide synthase (iNOS) enzyme, which is upregulated by Type 2 inflammatory cytokines, particularly interleukin-4 and interleukin-13 [10]. FeNO measurement provides a quantitative assessment of eosinophilic airway inflammation and has been shown to predict responsiveness to corticosteroid therapy, guide treatment decisions, and monitor disease control [11,12]. An elevated FeNO level (>50 parts per billion in adults and >35 parts per billion in children) is highly suggestive of corticosteroid-responsive asthma and can be particularly useful in patients without demonstrable bronchodilator reversibility [13]. Inducible laryngeal obstruction (ILO), formerly known as vocal cord dysfunction, is a condition characterized by inappropriate, transient, and reversible narrowing of the larynx during respiration, resulting in dyspnoea, stridor, and a sensation of throat tightness [14]. ILO frequently coexists with asthma and may be misdiagnosed as poorly controlled asthma, contributing to diagnostic and therapeutic challenges [15]. Dysfunctional breathing syndrome (DBS) encompasses a spectrum of breathing pattern disorders characterized by abnormal breathing mechanics, hyperventilation, and respiratory symptoms in the absence of identifiable organic pathology [16]. DBS frequently coexists with asthma and ILO, and may contribute to symptom persistence despite appropriate pharmacological therapy [17]. We present the case of a 17-year-old female with BAP1-TPDS who presented with chronic breathlessness, initially diagnosed as asthma but found to have concurrent allergic eosinophilic asthma, inducible laryngeal obstruction, and dysfunctional breathing. This case highlights the diagnostic complexity in patients with genetic syndromes presenting with common respiratory symptoms and emphasizes the importance of comprehensive assessment in this population.

Case Presentation

The patient is a 17-year-old young woman who was referred to the respiratory clinic for worsening breathlessness of approximately 4 years duration, during which time she had been diagnosed with asthma. The diagnosis itself had surrounding uncertainty due to the lack of confirmatory investigations such as pulmonary function testing. She had been managed with Symbicort (budesonide/formoterol) and salbutamol as required; however, she reported only mild symptomatic improvement with these medications. Her breathlessness occurred throughout the majority of the day, every day, and was worse with any physical activity. She described the sensation as "not being able to take a deep satisfying breath" and reported that she frequently had to consciously control her breathing. A flight of stairs was sufficient exertion to result in significant breathlessness requiring her to stop and recover. Interestingly, despite these symptoms, she remained capable of participating in competitive sports without major limitation, suggesting a discrepancy between her subjective symptom severity and objective functional capacity. The discrepancy in her symptoms suggested that the cause was unlikely to be explained by fixed pulmonary pathology alone. She denied wheeze, nocturnal symptoms, chronic cough, sputum production, chest pain, or symptomatic triggers related to weather, time of day, or environmental exposures.

Her family history was significant for the BAP-1 tumour pathogenic variant. The patient, her mother, and two of her siblings are carriers of the variant. Several family members have developed BAP-1-associated melanocytic tumours (BAPomas). Her maternal grandfather developed mesenteric mesothelioma, and her mother was previously diagnosed with meningioma. The patient herself had undergone 10-12 dermatological skin excisions for lesions and was undergoing MRI surveillance for a pituitary lesion found in early 2026. The family was well aware of the increased lifetime risk of uveal melanoma, cutaneous melanoma, renal malignancy, and mesothelioma. The patient was a never-smoker with no significant environmental or occupational exposures. She was studying full-time and was physically active, participating in competitive sports without significant functional limitation. There was no history of anxiety or depression, though she acknowledged that her breathing difficulties caused her significant distress and frustration. On examination, she was a well-appearing young woman in no acute distress. Vital signs were within normal limits, with oxygen saturation 98% on room air. Respiratory examination revealed clear breath sounds bilaterally with no wheeze, crackles, or prolonged expiration. There was no evidence of digital clubbing, cyanosis, or peripheral oedema. Cardiovascular and abdominal examinations were unremarkable. There was no palpable lymphadenopathy or hepatosplenomegaly.

Investigations

Imaging studies

Initially, a plain chest radiograph (posteroanterior and lateral views) was performed and was found to be entirely normal. Further imaging studies included a high-resolution computed tomography (HRCT) of the chest, which was also normal. These investigations revealed no mediastinal or hilar lymphadenopathy, pleural thickening, pleural plaques, pleural effusion, pulmonary nodules, emphysema, or interstitial lung disease. The lung parenchyma was normal, and there was no radiological evidence of air trapping on expiratory imaging. These findings were reassuring for any structural disease or pulmonary manifestations

of BAP-1 tumour predisposition syndrome. Abdominal ultrasound, performed as part of her BAP-1 surveillance, was also normal. The appearance of the liver, biliary tree, pancreas, spleen, and both kidneys lacked evidence of masses or abnormalities. The pituitary lesion detected on MRI in early 2026 was stable and being managed conservatively with ongoing surveillance.

Diagnostic Assessment

Pulmonary function testing

Parameter Pre-Bronchodilator Predicted (%) Post-Bronchodilator Predicted (%) Interpretation
FEV_1 3.43 L 98% 3.51 L 101% Normal
FVC 3.43 L 87% 3.58 L 91% Normal
FEV_1/FVC 1.00 100% 0.98 98% Normal
$FEF_{25–75}$ 3.21 L/s 85% 3.42 L/s 91% Normal
TLC 5.89 L 98% - - Normal
RV 2.17 L 146% - - Elevated
RV/TLC 37% 148% - - Mild physiological air trapping
DLCO 24.5 mL/min/mmHg 96% - - Normal
KCO 4.16 mL/min/mmHg/L 94% - - Normal; no interstitial lung disease

During her spirometry manoeuvres, the respiratory scientist noted glottic closure and significant difficulty in achieving prolonged expiration. This resulted in submaximal FVC measurements. Objectively, this was highly suggestive of inducible laryngeal obstruction (vocal cord dysfunction) and correlated clinically with her description of difficulty with deep inspiration. Her fractional exhaled nitric oxide (FeNO) measured 67.5 parts per billion, which indicated significant Type 2 eosinophilic airway inflammatory process and strongly supported corticosteroid-responsive asthma, despite the absence of bronchodilator reversibility.

Pathology

Haematology and Biochemistry:

- Full blood count: normal (haemoglobin 135 g/L, white cell counts 6.8 × 10^9/L, platelets 285 × 10^9/L)
- Inflammatory markers: C-reactive protein (CRP) 2.4 mg/L (within normal range)
- Erythrocyte sedimentation rate (ESR): 8 mm/h (within normal range)

Serum Markers:

- Serum angiotensin-converting enzyme (ACE): 28 U/L (negative)
- Rheumatoid factor: negative
- Anti-cyclic citrullinated peptide (anti-CCP) antibodies: negative

Autoimmune Screen:

- Antinuclear antibodies (ANA): negative
- Extractable nuclear antigens (ENA): negative
- Cytoplasmic anti-neutrophil cytoplasmic antibodies (C-ANCA): negative
- Perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA): negative
- Complement C3: 0.788 g/L (reference range: 0.9-1.8 g/L) — low
- Complement C4: 0.128 g/L (reference range: 0.1-0.4 g/L) — low

Allergy Testing:

- Total immunoglobulin E (IgE): 281 kIU/L (reference range: <100 kIU/L) — elevated
- Specific IgE to house dust mite (Dermatophagoides pteronyssinus): 61.9 kU/L (Class V, >50 kU/L) — marked sensitisation
- Specific IgE to grass pollen: negative
- Specific IgE to tree pollen: negative
- Specific IgE to animal allergens (cat, dog): negative
- Specific IgE to moulds: negative

Differential Diagnosis

Based on the clinical presentation, investigations, and the patient's genetic background, the following differential diagnoses were considered:

1. Allergic Eosinophilic Asthma

This was strongly supported by elevated FeNO (67.5 parts per billion) indicating Type 2 airway inflammation, elevated total IgE (281 kIU/L), marked house dust mite sensitisation (61.9 kU/L, Class V), and clinical response to inhaled corticosteroids, albeit incomplete. The absence of bronchodilator reversibility is not uncommon in well-controlled asthma or with suboptimal inhaler technique.

2. Inducible Laryngeal Obstruction (Vocal Cord Dysfunction)

This was supported by observation of glottic closure during spirometry, clinical correlation with her description of difficulty with deep inspiration, discrepancy between subjective symptom severity and objective functional capacity, and symptoms not typically responsive to bronchodilators.

3. Dysfunctional Breathing Syndrome

This was considered due to mild physiological air trapping with preserved lung function, breathlessness requiring conscious breathing control, symptoms present throughout the majority of the day, and lack of typical asthma triggers (wheeze, nocturnal symptoms, environmental triggers).

4. BAP-1 Tumour Predisposition Syndrome Without Pulmonary Involvement

This was considered because of known pathogenic BAP-1 variant with multiple family members affected, normal HRCT chest with

no evidence of mesothelioma, pulmonary nodules, or pleural disease, normal abdominal imaging with no evidence of renal malignancy, and the patient's respiratory symptoms being unlikely to be directly attributable to BAP-1-associated malignancy.

5. Complement-Mediated Autoimmune Process

This was considered due to low C3 and C4 levels in the absence of other autoimmune markers and potential association with immune dysregulation in the context of BAP-1 syndrome, though this has not been well-described in the literature.

6. Pituitary Lesion-Related Endocrine Dysfunction

This was considered due to known pituitary lesion found in early 2026 and potential for hormonal influences on respiratory function and perception of breathlessness. However, the lesion was stable and not associated with endocrine dysfunction.

Discussion

This case highlights several important clinical considerations at the intersection of genetic predisposition to malignancy and common respiratory disease. The patient's presentation with chronic breathlessness, initially attributed to asthma, ultimately revealed a more complex diagnostic picture requiring comprehensive assessment.

BAP-1 Tumour Predisposition Syndrome and Pulmonary Manifestations

The BAP-1 tumour predisposition syndrome is a well-characterized autosomal dominant condition associated with germline mutations in the BAP1 gene [2]. The syndrome is associated with an increased lifetime risk of multiple malignancies, including uveal melanoma (lifetime risk approximately 25%), cutaneous melanoma (lifetime risk approximately 20%), renal cell carcinoma (lifetime risk approximately 15%), and malignant mesothelioma (lifetime risk approximately 10%) [4,5]. Pulmonary manifestations of BAP1-TPDS are predominantly neoplastic, with malignant mesothelioma being the most common and best-described thoracic malignancy in affected individuals [5]. Other reported pulmonary neoplasms include atypical pulmonary carcinoid tumours, lung adenocarcinoma, and sarcomatoid carcinomas [18]. The diagnosis of BAP1-TPDS-associated mesothelioma typically occurs at a younger age compared to sporadic mesothelioma, with a mean age at diagnosis of approximately 50 years [5]. In this case, the patient's normal HRCT chest was reassuring and excluded structural pulmonary pathology, pleural disease, or pulmonary manifestations of BAP1-TPDS. However, the presence of chronic respiratory symptoms in a patient with BAP1-TPDS necessitated a thorough diagnostic evaluation to exclude BAP-1-associated malignancies and identify alternative pathologies.

Allergic Eosinophilic Asthma in the Context of BAP-1 Syndrome

The patient's elevated FeNO (67.5 parts per billion) is a well-established biomarker of Type 2 eosinophilic airway inflammation and predicts responsiveness to corticosteroid therapy [11,12]. FeNO levels greater than 50 parts per billion in adults and greater than 35 parts per billion in children are considered highly suggestive of eosinophilic airway inflammation and corticosteroid-responsive asthma [13]. The patient's FeNO of 67.5 parts per billion therefore provided strong evidence for allergic eosinophilic asthma. The mechanism by which FeNO becomes elevated in Type 2 inflammation involves the upregulation of inducible nitric oxide synthase (iNOS) in airway epithelial cells by Type 2 cytokines, particularly interleukin-4 and interleukin-13, which are produced by T-helper 2 cells and group 2 innate lymphoid cells [10]. Nitric oxide itself has diverse biological functions, including smooth muscle relaxation, vasodilation, and antimicrobial activity, but its elevated levels in asthmatic airways reflect the underlying inflammatory process [19]. Importantly, FeNO measurement is particularly useful in clinical scenarios where diagnostic uncertainty exists, such as in patients without demonstrable bronchodilator reversibility or those with atypical symptoms [20]. In this case, the elevated FeNO provided objective evidence of corticosteroid-responsive asthma that would otherwise have been missed based on spirometry alone.

The marked sensitisation to house dust mite (D. pteronyssinus) with specific IgE of 61.9 kU/L (Class V) further supported the diagnosis of allergic asthma. House dust mite sensitisation is one of the most common aeroallergen triggers in asthma and is associated with more severe disease, increased healthcare utilisation, and reduced quality of life [21]. The elevated total IgE (281 kIU/L) was consistent with an atopic phenotype and supported the diagnosis of allergic asthma. Interestingly, the patient did not demonstrate significant bronchodilator reversibility on spirometry, which is a criterion for the diagnosis of asthma according to some guidelines [6]. However, the absence of bronchodilator reversibility does not exclude asthma, particularly in patients who are already on inhaled corticosteroids or who have well-controlled disease [22]. Furthermore, the presence of significant FeNO elevation and specific IgE sensitisation provided sufficient evidence for the diagnosis of allergic eosinophilic asthma, even in the absence of bronchodilator reversibility. The relationship between BAP-1 syndrome and allergic asthma is not well-established, and no direct pathogenic link has been identified. The co-occurrence of BAP1-TPDS and allergic asthma in this case is likely coincidental, though it is possible that immune dysregulation associated with BAP-1 mutation may influence the development

of allergic disease. Further research would be needed to explore this potential association.

Inducible Laryngeal Obstruction

The observation of glottic closure during spirometry manoeuvres provided objective evidence of inducible laryngeal obstruction (ILO), a condition characterised by inappropriate adduction of the vocal cords during inspiration or expiration, resulting in airflow obstruction at the level of the larynx [14]. ILO is frequently misdiagnosed as asthma and may coexist with asthma, contributing to symptom persistence despite appropriate asthma therapy [15]. The patient's clinical features were consistent with ILO, including sensation of difficulty with deep inspiration, conscious control of breathing, discrepancy between subjective symptom severity and objective functional capacity, absence of wheeze or other typical asthma symptoms, and glottic closure observed during spirometry. The prevalence of ILO in patients with asthma is estimated to be 10-20%, and the condition is more common in adolescent females, athletes, and individuals with underlying psychological stress [23]. The patient's demographic (young female, athlete) and clinical features were therefore consistent with ILO.

The pathophysiology of ILO involves inappropriate laryngeal adduction during respiration, which may be triggered by various factors including exercise, irritant exposure, emotional stress, or laryngeal hypersensitivity [24]. In athletes, ILO may be particularly problematic as it can significantly impact performance and is often misdiagnosed as exercise-induced bronchoconstriction [25]. The management of ILO includes speech therapy, respiratory retraining, and psychological support [26]. Speech pathology intervention focuses on identifying and modifying inappropriate laryngeal behaviours through techniques such as respiratory retraining, laryngeal control exercises, and relaxation strategies [27]. In this case, the patient was referred for speech pathology assessment and respiratory physiotherapy for breathing retraining.

Dysfunctional Breathing Syndrome

Dysfunctional breathing syndrome (DBS) encompasses a spectrum of breathing pattern disorders characterized by abnormal breathing mechanics, hyperventilation, and respiratory symptoms in the absence of identifiable organic pathology [16]. DBS frequently coexists with asthma and ILO and may contribute to symptom persistence despite appropriate therapy [17]. The patient's breathlessness, which required conscious breathing control and was present throughout the majority of the day, was consistent with DBS. The mild physiological air trapping observed on pulmonary function testing may have been related to breathing pattern abnormalities rather than intrinsic airway disease. The normal DLCO and KCO excluded interstitial lung disease and suggested that the air trapping was likely physiological rather than pathological. The pathophysiology of DBS is complex and may involve abnormal breathing patterns, such as thoracic breathing, hyperventilation, and breath-holding, which can lead to respiratory symptoms, anxiety, and functional impairment [28]. The relationship between DBS and psychological factors is well-established, with anxiety and stress frequently contributing to the development and maintenance of abnormal breathing patterns [29]. The management of DBS includes breathing retraining, relaxation techniques, and addressing any underlying psychological factors [30]. The patient was referred for respiratory physiotherapy for breathing retraining and education on diaphragmatic breathing techniques.

Complement Abnormalities

The patient's low C3 (0.788 g/L) and C4 (0.128 g/L) levels were an incidental finding that raised the question of complement-mediated disease. Low C3 and C4 levels can occur in autoimmune diseases such as systemic lupus erythematosus (SLE), where complement activation leads to consumption of complement components [31]. However, the patient's negative autoimmune screen (ANA, ENA, ANCA) made SLE and other autoimmune conditions unlikely. Alternatively, low complement levels may be due to inherited complement deficiencies, which are associated with an increased risk of autoimmune disease and infection [32]. Complement component deficiencies are rare, and the clinical significance of isolated low C3 and C4 levels in this patient is unclear.

Another possibility is that the low complement levels represent complement consumption associated with BAP-1-related immune dysregulation. The BAP-1 protein is involved in the regulation of immune responses, and BAP-1 mutations have been associated with altered immune function [33-37]. However, this association has not been well-characterized and further investigation would be needed. Given the patient's low C3 and C4 levels in the context of a negative autoimmune screen and no clinical evidence of autoimmune disease, we recommended rheumatology consultation for further evaluation. Monitoring of complement levels over time and assessment for the development of autoimmune symptoms were also recommended.

Clinical Implications and Management Considerations

This case has several important clinical implications:

- Comprehensive Diagnostic Assessment in BAP-1 Patients: Patients with BAP1-TPDS presenting with respiratory symptoms require thorough diagnostic evaluation to exclude BAP-1-associated malignancies and identify alternative pulmonary pathologies. This includes high-resolution chest imaging, pulmonary function testing, and assessment for conditions such as asthma, ILO, and DBS.

- Role of FeNO in Diagnostic Assessment: FeNO measurement is a valuable tool in the assessment of breathlessness in patients with suspected asthma. Elevated FeNO (>50 parts per billion) predicts responsiveness to corticosteroid therapy and can guide treatment decisions, particularly in patients without demonstrable bronchodilator reversibility. The non-invasive nature of FeNO measurement and its ability to provide real-time information about airway inflammation make it an attractive diagnostic tool in clinical practice.
- Recognition of ILO and DBS: The coexistence of asthma, ILO, and DBS is common and should be considered in patients with persistent respiratory symptoms despite appropriate asthma therapy. Observation of glottic closure during spirometry and the presence of characteristic symptoms should prompt referral for speech therapy and respiratory physiotherapy.
- Multidisciplinary Care: The management of patients with BAP1-TPDS and complex respiratory symptoms requires a multidisciplinary approach involving respiratory physicians, geneticists, speech pathologists, respiratory physiotherapists, and psychologists.

Clinical Management Plan

Pharmacological Management:

- Escalation of inhaler therapy to triple therapy (LABA/LAMA/ICS) with reinforcement of inhaler technique and adherence
- Consideration of add-on therapy with leukotriene receptor antagonists or macrolide antibiotics if symptom control remains inadequate
- Potential for biologic therapy (anti-IgE, anti-IL-5, or anti-IL-4/13) if Type 2 inflammation persists despite optimal inhaled therapy

Non-Pharmacological Management:

Strict house dust mite avoidance measures:

- Allergen-impermeable mattress and pillow cover
- Regular hot washing of bedding (≥60°C)
- Minimizing dust exposure through frequent vacuuming with HEPA filters
- Maintaining indoor humidity below 50%
- Speech pathology assessment and therapy for ILO
- Respiratory physiotherapy for breathing retraining
- Consideration of regular intranasal corticosteroids should upper airway allergic symptoms develop, with potential for otolaryngologist collaboration

Surveillance:

- Ongoing BAP-1 surveillance as per established protocols
- Monitoring of pituitary lesion with MRI as per neurosurgical recommendations
- Regular review of respiratory symptoms and inhaler technique
- Monitoring of complement levels and assessment for autoimmune symptoms

Study Limitations

This case study has several limitations that should be acknowledged. First, as a single case report, it may not reflect the spectrum of patient presentations with similar genetic conditions or respiratory pathologies. Second, the patient's symptoms and response to treatment have been described over a limited period, and long-term outcomes are not available. Third, the patient's young age and the presence of multiple comorbidities (BAP1-TPDS, allergic asthma, ILO, DBS) make generalization to other patient populations difficult. Despite these limitations, this case provides valuable insight into the diagnostic evaluation and management of respiratory symptoms in patients with BAP1-TPDS. The case highlights the importance of comprehensive assessment, the utility of biomarkers such as FeNO, and the recognition of coexisting conditions such as ILO and DBS.

Further research is needed to:

- Characterise the spectrum of respiratory conditions in patients with BAP1-TPDS
- Explore potential associations between BAP-1 mutations and immune dysregulation
- Evaluate the efficacy of targeted therapies for allergic asthma in patients with BAP1-TPDS
- Investigate the prevalence and clinical significance of complement abnormalities in BAP1-TPDS

Conclusion

This case demonstrates that respiratory symptoms in patients with BAP-1 tumour predisposition syndrome may arise from common respiratory conditions such as allergic eosinophilic asthma and inducible laryngeal obstruction, rather than from BAP-1-associated malignancies. The elevated FeNO level provided crucial diagnostic information, confirming Type 2 eosinophilic airway inflammation and supporting corticosteroid-responsive asthma despite the absence of bronchodilator reversibility. A multidisciplinary approach incorporating comprehensive pulmonary function testing, FeNO measurement, and assessment for inducible laryngeal obstruction is essential for accurate diagnosis and management. The presence of low complement levels in this patient warrants further investigation for potential autoimmune or complement-mediated processes. This case highlights the importance of comprehensive diagnostic evaluation

in patients with genetic syndromes presenting with respiratory symptoms and provides a framework for the management of such patients.

Learning Points

- BAP-1 tumour predisposition syndrome is associated with an increased risk of multiple malignancies, including mesothelioma, renal carcinoma, and melanoma. However, respiratory symptoms in affected patients may arise from common respiratory conditions unrelated to their genetic predisposition.
- Comprehensive diagnostic assessment including high-resolution chest imaging, pulmonary function testing, and FeNO measurement is essential to exclude BAP-1-associated malignancies and identify alternative pulmonary pathologies.
- Elevated FeNO (>50 parts per billion) is a reliable biomarker of Type 2 eosinophilic airway inflammation and predicts corticosteroid responsiveness. FeNO measurement is particularly useful in patients without demonstrable bronchodilator reversibility and provides objective evidence of airway inflammation that can guide treatment decisions.
- Inducible laryngeal obstruction (vocal cord dysfunction) frequently coexists with asthma and should be suspected in patients with persistent respiratory symptoms despite appropriate therapy, particularly when associated with difficulty taking a deep breath and observed glottic closure during spirometry.
- Dysfunctional breathing syndrome is a common cause of persistent breathlessness and should be considered in patients with breathing pattern abnormalities and preserved lung function. Breathing retraining and physiotherapy are important components of management.
- Complement abnormalities may occur in patients with BAP1-TPDS and warrant further investigation for autoimmune conditions or complement deficiencies, though the clinical significance of these findings is not well-established.
- Multidisciplinary care involving respiratory physicians, geneticists, speech pathologists, and physiotherapists is essential for optimal management of patients with complex respiratory symptoms and genetic conditions.

Declarations

Patient Consent: Written informed consent was obtained from the patient and her parent/guardian for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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Author Contributions

- Pranav Kumar: Conceptualization of the case report; clinical management of the patient; interpretation of radiological, pathology, and microbiological findings; literature review; manuscript preparation and critical revision.
- Ashley Fisser: Contributed to interpretation of radiological findings, assisting with literature review, clinical management, and writing of the case report, manuscript preparation and critical revision.

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