Case Report

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Pathology Section

NF1 with Ewing's Sarcoma and Thoracopulmonary PNET with Gastrointestinal Neoplasm: A Case Report of Synchronous Malignancies

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ABSTRACT

Synchronous malignancies are rare and pose significant diagnostic and therapeutic challenges due to their complex presentations and diverse aetiologies. This report highlights two unique cases emphasising the importance of a multidisciplinary approach to management. The first case involves a 24-year-old male with Neurofibromatosis type 1 (NF1), presenting with Ewing's sarcoma affecting the rib and lung. NF1, a genetic disorder caused by mutations in the NF1 gene, predisposes individuals to various malignancies, including sarcomas. This patient exhibited characteristic NF1 features such as café-au-lait spots, multiple neurofibromas, and Lisch nodules. Imaging revealed a destructive thoracic mass and histopathology, supported by immunohistochemistry, confirmed the diagnosis of Ewing's sarcoma. The patient underwent surgical resection followed by chemotherapy, resulting in a favourable outcome. The second case describes a 75-year-old chronic smoker who presented with thoracopulmonary Primitive Neuroectodermal Tumour (PNET) and a high-grade dysplastic adenomatous polyp in the cecum. Imaging and histological evaluations confirmed the coexistence of these malignancies. The thoracic tumour was surgically resected and treated with a chemotherapy regimen, while the gastrointestinal lesion required a hemicolectomy. The patient's postoperative course was uneventful, and follow-up assessments revealed no residual disease. These cases underscore the pivotal role of integrating advanced imaging, targeted biopsies, and molecular diagnostics to accurately identify and manage synchronous malignancies. Genetic predispositions, such as NF1, and environmental factors, including smoking, highlight the interplay of inherited and acquired risk factors in multifocal tumourigenesis. Multidisciplinary collaboration and individualised treatment strategies are critical for optimising patient outcomes, particularly in complex cases like these.

Keywords: Ewing's sarcoma, Genetic risk, Integrated diagnostic approach, Multiple primary cancers, Neurofibromatosis type 1 (NF1), Thoracopulmonary PNET

CASE REPORT

Case 1

A 24-year-old male, previously diagnosed with NF1, presented with a one-month history of progressively worsening shortness of breath, non-productive cough, and left-sided chest pain. His NF1 diagnosis was confirmed through multiple cutaneous neurofibromas and café-au-lait spots, in line with NIH diagnostic criteria. Genetic testing was not performed due to resource limitations, and differential diagnoses such as schwannomatosis and other RASopathies were ruled out based on clinical and imaging findings. The patient also had a history of recurrent seizures over the past three years, controlled with antiepileptic medications. A positive family history of seizure disorders was noted, as his biological father had experienced similar episodes.

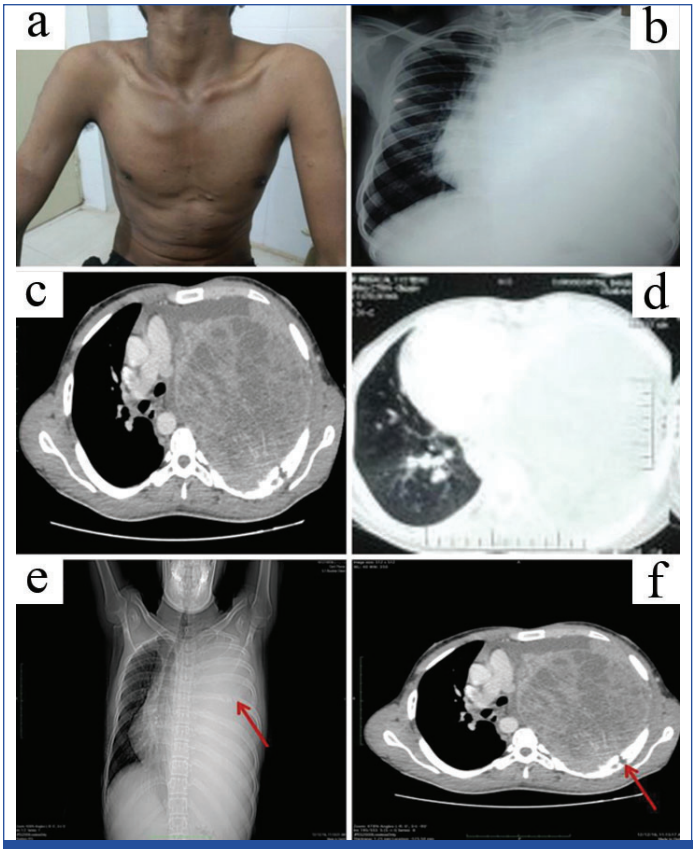
On physical examination, the patient appeared mildly distressed due to dyspnea. Multiple subcutaneous nodules and hyperpigmented macular lesions were scattered over the trunk and upper limbs, consistent with NF1 manifestations. A visible protrusion of the left anterior chest wall [Table/Fig-1a] created asymmetry. Palpation revealed a firm, non-tender mass on the left anterior chest, suggesting rib involvement. Lung auscultation disclosed decreased breath sounds on the left-side and increased vocal resonance, while percussion revealed dullness over the left hemithorax, suggesting pleural effusion.

Further evaluation revealed a mediastinal shift with tracheal deviation and displacement of the cardiac apex to the right fifth intercostal space. Chest X-rays [Table/Fig-1b] showed an opaque left hemithorax with tracheal and cardiac displacement to the right. CECT scans [Table/Fig-1c,d] demonstrated a large, heterogeneous mass occupying the left hemithorax, causing mediastinal structure displacement. Additionally, lytic destruction of the left sixth rib was evident [Table/Fig-1e], and left pleural effusion with nodular pleural deposits was identified [Table/Fig-1f].

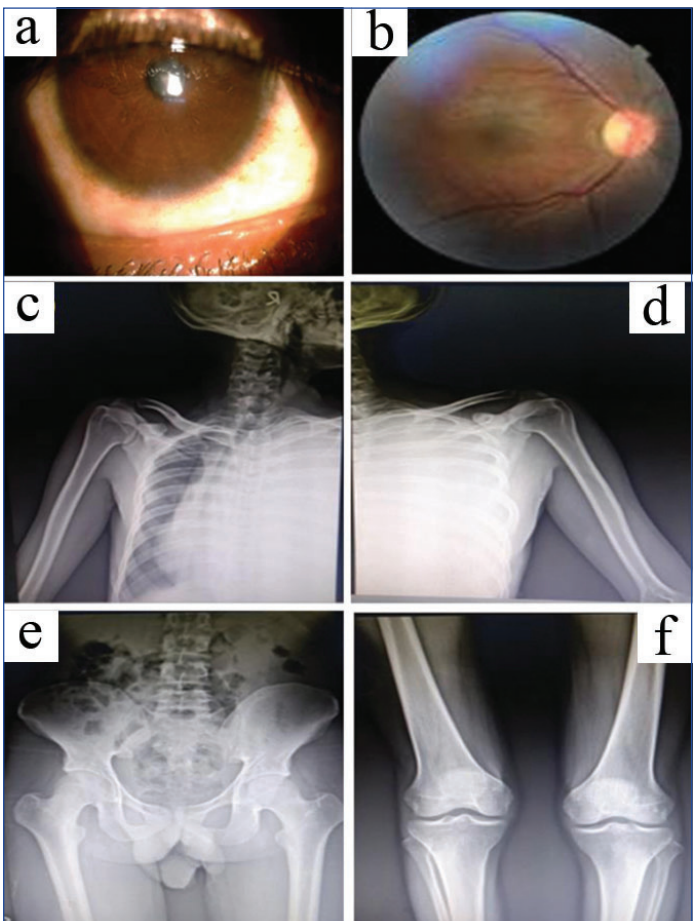
Thoracocentesis yielded haemorrhagic pleural fluid. Cytology revealed small, round, atypical cells in rosette-like formations, suggestive of a small round cell tumour. Core biopsy findings confirmed sheets of small, round, blue cells with high nuclear-to-cytoplasmic ratios, consistent with a neuroectodermal-origin tumour. Further NF1-related manifestations included ocular findings such as Lisch nodules [Table/Fig-2a] and potential optic nerve glioma [Table/Fig-2b]. Skeletal abnormalities, revealed through X-rays, included cervical spine deformities [Table/Fig-2c], thoracic region abnormalities [Table/Fig-2d], pelvic bone irregularities [Table/Fig-2e], and knee bone structure disparities [Table/Fig-2f]. Immunohistochemical (IHC) staining showed strong nuclear positivity for FLI-1 [Table/Fig-3a], a high MIB-1 index of 40% [Table/Fig-3b], and moderate Synaptophysin positivity [Table/Fig-3c] supporting the diagnosis of Ewing's sarcoma. NKX2.2, a more specific marker for Ewing's sarcoma, was unavailable and is noted as a limitation.

A multidisciplinary tumour board, involving specialists in oncology, pathology, radiology, and neurology, confirmed the diagnosis of Ewing's sarcoma involving the left sixth rib and adjacent lung, in the context of NF1 and seizure disorder.

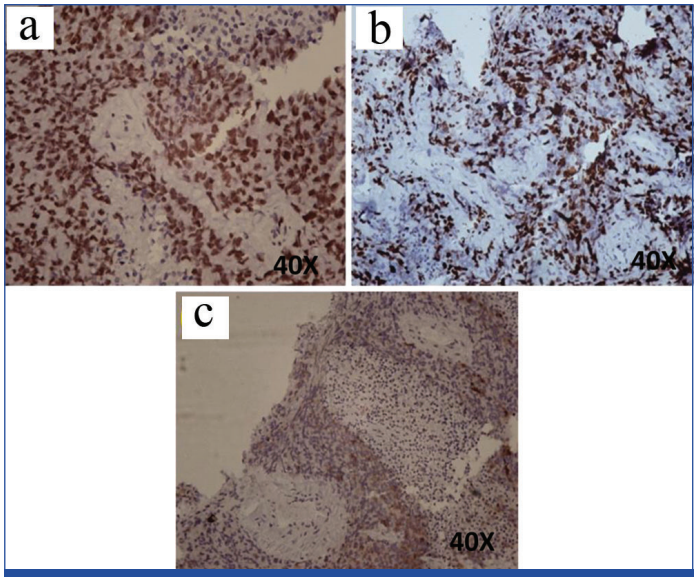
This case exemplifies the complexities associated with diagnosing and managing multiple primary malignancies in elderly patients with significant risk factors, such as chronic smoking. The synchronous



[Table/Fig-1]: a) showing noticeable protrusion of the left anterior chest wall, accompanied by a complete shift of the trachea to the right; b) chest X-ray reveals an opaque left hemithorax with the trachea and heart both displaced to the right-side; c,d) shows CECT scans demonstrating a large, heterogeneously dense mass filling the left hemithorax and causing a shift of mediastinal structures to the right; e) chest X-ray, showing lytic destruction of the left sixth rib; f) CECT displays left pleural effusion and nodular pleural deposits, as pointed out by the arrow.



[Table/Fig-2]: a) shows an ocular Lisch nodule; b) captures a possible optic nerve glioma. X-ray images in c&d) reveal skeletal abnormalities in the cervical spine and thoracic region, respectively; e) presents pelvic bone irregularities; and f) illustrates disparities in the knees' bone structure.



[Table/Fig-3]: Immunohistochemical (IHC) staining a) (40X) showing FLI 1 Strong positive; b) (40X) shows MIB index- 40%; c) (40X) shows Synaptophysin moderate positive.

occurrence of a pulmonary malignancy, specifically thoracopulmonary PNET, alongside high-grade dysplastic adenomatous changes in the cecum, underscores the need for thorough clinical evaluation and a multidisciplinary diagnostic approach. Advanced imaging, coupled with targeted biopsies, was essential in accurately identifying and differentiating the distinct malignancies present in this patient.

Therapeutic intervention and follow-up: Given the concurrent presentation of thoracic and abdominal malignancies, a comprehensive treatment plan was initiated. The thoracic mass, identified as thoracopulmonary PNET- a rare variant within the Ewing's sarcoma family- required prompt surgical intervention. The patient underwent a left thoracotomy with resection of the third rib mass. Postsurgery, he was started on a chemotherapy regimen comprising Vincristine, Adriamycin, and Cyclophosphamide (VAC), which is the standard approach for treating Ewing's sarcoma. Simultaneously, the gastrointestinal malignancy required a separate management plan. A hemicolectomy was proposed to address the rectal mass, aiming for complete resection of the tumour. The occurrence of thoracopulmonary PNET alongside a primary gastrointestinal neoplasm is rare and presents a complex clinical scenario. It necessitates a detailed diagnostic process to differentiate between metastatic disease and truly synchronous primary malignancies.

This case underscores the diagnostic and therapeutic challenges associated with synchronous malignancies, particularly in older patients. The co-occurrence of thoracopulmonary PNET and a gastrointestinal malignancy in a geriatric patient not only highlights the need for vigilance but also emphasises the value of a systematic, step-by-step approach to diagnosis and treatment. Early intervention, guided by a coordinated, multidisciplinary team, was crucial for this patient's management and significantly improved the overall prognosis.

Case 2

Patient Demographics and Clinical History

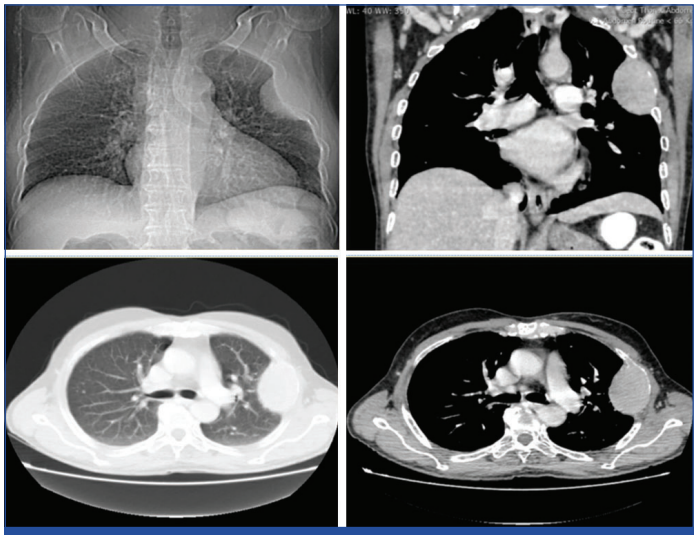
A 75-year-old male with a 50-year history of chronic smoking presented with severe breathlessness (MMRC Grade 3) and persistent, intense left-sided chest pain that disrupted his sleep over the past month. He denied symptoms such as weight loss, haemoptysis, or night sweats. His medical history was otherwise unremarkable, with no prior diagnoses of tuberculosis or diabetes. Additionally, he reported gastrointestinal discomfort, including diffuse abdominal pain persisting for one month and constipation for the past 20 days.

Physical Examination

On examination, the patient was febrile (98.4°F), tachycardic (96 beats/min), hypertensive (138/80 mmHg), and tachypneic (29 breaths/min) with oxygen saturation of 92% on room air. Respiratory assessment revealed tenderness over the left second and third ribs and diffuse rhonchi bilaterally. Abdominal examination identified tenderness in the right iliac fossa, without palpable masses.

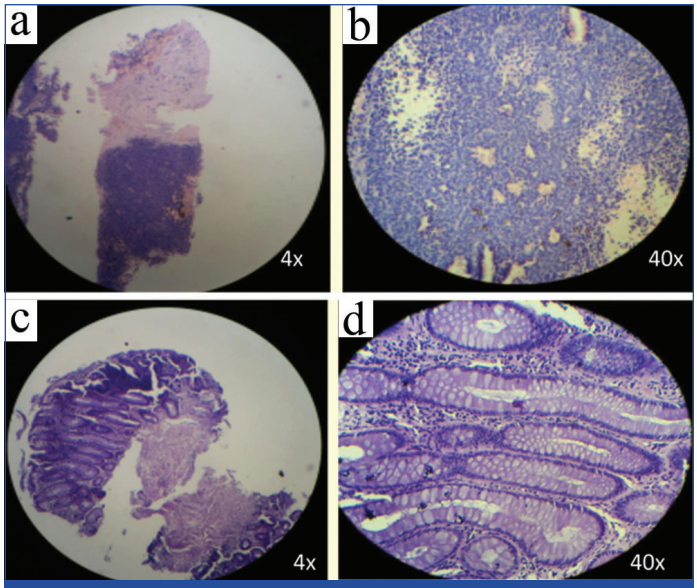
Diagnostic Focus and Assessment

The patient presented with significant anaemia, indicated by a haemoglobin level of 9 g/dl, necessitating an urgent diagnostic work-up. Imaging studies were prioritised due to the severity of his symptoms. Chest radiography revealed a homogenous opacity in the left upper lung zone [Table/Fig-4a], suggesting the presence of a pulmonary lesion. To further evaluate this finding, a Contrast-Enhanced Computed Tomography (CECT) scan of the thorax was performed, which demonstrated a heterogeneous mass involving the left third rib [Table/Fig-4b,c]. The imaging also revealed pleural effusion and nodular pleural deposits [Table/Fig-4d], along with regional lymphadenopathy, consistent with a suspected malignant process. Based on these findings, an ultrasound-guided biopsy of the lung mass was conducted.



[Table/Fig-4]: a) Chest X-ray: showing homogeneous opacity in the left upper chest; b) Coronal CECT: Shows a homogeneous lung mass associated with erosion of the left third rib; c) Axial CECT (lung level): Reveals a well-defined mass in the periphery of the left lung; d) Axial CECT (rib level): Demonstrates erosion of the left third rib by the adjacent mass, suggesting an aggressive lesion, possibly malignant. (Images from left to right)

Histopathological analysis of the biopsy specimen revealed a mix of bronchoalveolar tissue and tumour cells with hyperchromatic nuclei. IHC staining showed the tumour cells were positive for CD99 but negative for Neuron-Specific Enolase (NSE), supporting the diagnosis of PNET, a rare subtype of the Ewing's sarcoma family of tumours. Further evaluation of the gastrointestinal tract was prompted by an abdominal ultrasound, which revealed thickening of the cecal wall [Table/Fig-5a]. A colonoscopy identified a small mass in the cecum [Table/Fig-5b]. Biopsy findings confirmed high-grade dysplastic changes within an adenomatous polyp [Table/Fig-5c]. Surgical resection of the lesion was performed, and histopathological examination of the excised tissue confirmed the presence of premalignant changes with clear surgical margins, ruling out invasive carcinoma [Table/Fig-5d]. These findings highlighted the coexistence of synchronous malignancies, including a thoracopulmonary tumour and a premalignant gastrointestinal condition, necessitating a multidisciplinary approach to diagnosis and management. The integration of imaging, histopathology, and immunohistochemistry proved critical in accurately identifying and differentiating the distinct malignancies affecting this patient.



[Table/Fig-5]: a) (4X): Trucut Biopsy (Lung Tissue): Displays fibrocollagenous tissue with embedded tumour tissue; b) (40X) showing tumour Cytology: Shows medium-sized round cells with hyperchromatic nuclei, inconspicuous nucleoli, and occasional mitotic figures. Nuclear molding, rosette-like structures, and perivascular condensation are present, features often associated with small round cell tumours; c) (4X) Histopathology of adenomatous polyp with dysplasia; d) (40X): further magnification of the adenomatous polyp with dysplasia.

Follow-up and Outcome

The patient underwent a left thoracotomy with resection of the third rib to treat the thoracopulmonary PNET. Post-surgical histopathology confirmed the diagnosis, and chemotherapy with the VAC regimen was initiated. The treatment was well-tolerated, with no significant side effects reported. The gastrointestinal lesion, identified as a high-grade dysplastic adenomatous polyp was successfully managed with a laparoscopic hemicolectomy. Surgical analysis confirmed clear margins, and no invasive carcinoma was detected. Regular follow-up colonoscopies were planned to monitor for recurrence or new lesions.

At three months, imaging studies showed no residual thoracic disease, and follow-up colonoscopy revealed no new abnormalities. The patient's symptoms, including breathlessness and chest pain, had resolved. Smoking cessation efforts were successful, and the patient reported abstinence. Nutritional support and iron supplementation improved his anaemia. Six months post-treatment the patient remained disease-free with a significant improvement in quality of life. Regular surveillance with imaging and colonoscopy continues to ensure early detection of any recurrence.

DISCUSSION

Synchronous malignancies present significant challenges in clinical practice, particularly when genetic predispositions intersect with lifestyle factors, complicating both diagnosis and management [1]. These rare occurrences demand heightened clinical vigilance and a collaborative, multidisciplinary approach to ensure timely identification and effective treatment. This report highlights two rare and instructive cases, emphasising the need for tailored diagnostic strategies and personalised therapeutic interventions for patients with multiple primary cancers.

The first case involves a young adult with NF1 and a history of seizures, presenting with Ewing's sarcoma affecting the rib and lung. NF1, a genetic disorder with a global prevalence of approximately 1 in 3,000 individuals, manifests across a spectrum ranging from benign neurofibromas to malignant tumours, adding complexity to early diagnosis [2]. Ewing's sarcoma, a small round blue cell tumour primarily affecting young adults, has an incidence of about 200 cases annually in the United States, with the majority presenting in bone or soft tissue. The co-occurrence of NF1 and Ewing's sarcoma is exceedingly rare, with fewer than 10 cases documented in the literature, further complicating clinical evaluation and management.

The second case features an elderly smoker diagnosed with a thoracopulmonary PNET, a rare and aggressive malignancy within the Ewing's sarcoma family [3]. Thoracopulmonary PNET is even less common than Ewing's sarcoma, with only a limited number of cases reported globally. Its nonspecific symptoms and aggressive nature make diagnosis challenging. This patient also had a concurrent gastrointestinal neoplasm, further complicating the diagnostic process. Differentiating between synchronous primary malignancies and metastatic disease is critical, as it significantly influences both treatment strategies and prognosis.

Synchronous malignancies, particularly those involving NF1, Ewing's sarcoma, and thoracopulmonary PNET, highlight the importance of a meticulous diagnostic approach. Accura te differentiation between benign and malignant growths in NF1, as well as the identification of primary tumours in complex cases like the elderly smoker, is essential for optimising treatment outcomes. Advanced diagnostic techniques, including imaging modalities, targeted biopsies, and IHC analyses, play a pivotal role in these evaluations [4].

These cases underscore the necessity of personalised treatment approaches that account for the patient's genetic predisposition, lifestyle factors, and environmental exposures. Such tailored interventions enable the delivery of precise and effective therapies, improving patient outcomes and quality of life. Moreover, the indispensable role of multidisciplinary collaboration in managing complex oncological scenarios cannot be overstated. Close cooperation between oncology, pathology, radiology, and genetics specialists fosters comprehensive care and the development of innovative diagnostic and therapeutic strategies. Documenting and analysing such rare cases contributes to the growing body of medical literature, offering insights that refine diagnostic criteria and treatment protocols for similar cases in the future [4].

This report illustrates two unique instances of synchronous malignancies: NF1 associated with Ewing's sarcoma and a thoracopulmonary PNET coexisting with a gastrointestinal neoplasm. While rare, these cases emphasise the importance of understanding the interplay of genetic, environmental, and molecular factors in the development of multiple primary malignancies. This discussion explores these elements, providing a clear perspective on how they contribute to the emergence of such complex cancer presentations.

Genetic Factors and Tumourigenesis

Neurofibromatosis Type 1 (NF1) and synchronous cancers: NF1 Gene Mutation: NF1 is a genetic disorder caused by mutations in the NF1 gene, which is responsible for producing neurofibromin, a protein that regulates cell growth by controlling the Ras signaling pathway. Neurofibromin acts as a tumour suppressor by keeping cell proliferation in check. However, mutations in the NF1 gene lead to a loss of neurofibromin function, resulting in uncontrolled Ras activation, which promotes abnormal cell growth. This predisposes patients with NF1 to a range of tumours, including benign neurofibromas and various malignancies like sarcomas [5].

Ras-MAPK Pathway Activation: The Ras-MAPK pathway is a key player in cellular proliferation. When hyperactivated due to NF1 mutations, this pathway drives malignant transformation by promoting rapid cell division and survival. This mechanism not only increases the risk of developing benign neurofibromas but also predisposes NF1 patients to more aggressive sarcomas, such as Ewing's sarcoma [6]. The genetic background of NF1 patients thus sets the stage for the concurrent development of multiple malignancies, each driven by overlapping but distinct genetic changes [7].

Genetic Instability and Accumulating Mutations: Patients with NF1 often experience genetic instability, meaning their cells accumulate DNA damage more rapidly than those in the general population. This instability results from deficient DNA repair mechanisms and creates a permissive environment for additional mutations that can lead to other malignancies [8]. As a result, the coexistence of NF1 and Ewing's sarcoma may not only be due to a genetic predisposition but also due to ongoing mutational events that promote multiple tumour formations [9].

Ewing's Sarcoma and Genetic Drivers

EWS-FLI1 fusion gene: Ewing's sarcoma is primarily driven by the EWS-FLI1 fusion gene, a translocation event between chromosomes 11 and 22. This fusion gene acts as an aberrant transcription factor, activating oncogenic pathways that disrupt normal cell differentiation and promote malignant growth. It is a critical factor in the pathogenesis of Ewing's sarcoma and may enhance susceptibility to synchronous malignancies in genetically predisposed individuals like those with NF1 [10].

Epigenetic alterations: In addition to genetic mutations, epigenetic modifications contribute significantly to cancer development. The EWS-FLI1 fusion protein can alter the epigenetic landscape, reprogramming cells toward oncogenic behaviour. These epigenetic changes may extend beyond the site of the primary tumour, increasing the likelihood of additional malignancies. In NF1 patients, these epigenetic alterations could be more pronounced due to their inherent genetic instability, explaining the concurrent appearance of multiple cancers like Ewing's sarcoma [11].

Environmental and Lifestyle Contributions

Impact of smoking on multifocal tumourigenesis: Carcinogenic effects of smoking: Smoking is a well-established carcinogen that promotes DNA damage, oxidative stress, and chronic inflammation. Long-term exposure to tobacco carcinogens is associated with mutations in key genes, including tumour suppressor genes and oncogenes, across various tissues. This can result in the development of multiple primary tumours within the same individual [12].

Role of inflammation: Chronic inflammation induced by smoking creates a pro-tumourigenic microenvironment. This environment promotes angiogenesis, immune evasion, and tumour invasion, thereby increasing the likelihood of synchronous malignancies. In the case of Askin's tumour co-occurring with gastrointestinal cancer, inflammation likely played a central role in facilitating tumour development at multiple sites, underscoring the impact of smoking in multifocal cancer risk [13].

Immunosuppression from Smoking

Compromised immune surveillance: Smoking is also known to impair immune surveillance, reducing the body's ability to detect and destroy abnormal cells effectively. This immune compromise can contribute to the concurrent emergence of different primary malignancies, such as the coexistence of Askin's tumour in the chest wall and a gastrointestinal malignancy. Without robust immune monitoring, abnormal cells are more likely to evade detection and progress into malignant growths at multiple sites [14].

Molecular and Cellular Mechanisms in Synchronous Cancers

Genomic Instability and Defective DNA Repair

DNA repair deficiency: Genomic instability is a hallmark of cancer and is often seen in patients with genetic predispositions like NF1 and in those exposed to environmental carcinogens like smoking. Defective DNA repair mechanisms lead to an accumulation of mutations, which can manifest as multiple primary malignancies. For example, in NF1 patients, impaired DNA repair combined with smoking-induced DNA damage creates an environment highly conducive to the simultaneous development of distinct cancers [15].

Tumour Microenvironment (TME) influence: The tumour microenvironment plays a crucial role in the growth and spread

of malignancies. Factors such as cytokine secretion, immune cell infiltration, and changes in extracellular matrix components create a supportive environment for tumour growth. In the presence of multiple risk factors, the TME can facilitate the development of separate primary tumours, as seen in the coexistence of Askin's tumour and gastrointestinal malignancy [16].

Epigenetic Reprogramming

Epigenetic regulation of oncogenes: In addition to genetic mutations, epigenetic changes such as DNA methylation, histone modifications, and altered microRNA expression play critical roles in tumourigenesis. Epigenetic reprogramming can create a "field effect," promoting cancer development in nearby or unrelated tissues. For example, the epigenetic modifications driven by the EWS-FLI1 fusion gene in Ewing's sarcoma may alter the expression of genes involved in cell proliferation and differentiation across multiple tissues, potentially leading to synchronous tumours [17].

Shared epigenetic signatures: Studies suggest that cancers originating in different tissues may share similar epigenetic signatures. In patients like those with NF1, genetic predisposition coupled with epigenetic changes could enhance the risk of developing multiple primary malignancies. This explains why tumours that seem unrelated, like Ewing's sarcoma and neurofibromas, can co-exist within the same patient [18].

Implications for Clinical Practice

Genetic and molecular diagnostics: Understanding the genetic and epigenetic drivers of synchronous malignancies emphasises the importance of comprehensive genetic screening, especially in patients with known genetic disorders like NF1 or high-risk lifestyles like chronic smoking. Advanced molecular diagnostics, such as next-generation sequencing and epigenetic profiling, should be employed to detect early signs of multiple malignancies and tailor treatment strategies accordingly [19].

Preventive approaches: For high-risk patients, preventive strategies should include lifestyle modifications, routine screenings, and early genetic counseling. In NF1 patients, proactive monitoring for potential secondary malignancies is essential, while in smokers, aggressive smoking cessation efforts can significantly reduce the risk of multifocal cancers [20].

CONCLUSION(S)

The development of synchronous malignancies is driven by a complex interplay of genetic mutations, environmental exposures, and molecular alterations. In patients with predisposing factors like NF1 or long-term smoking, the risk of concurrent cancers increases significantly. The insights from this case series underscore the importance of a comprehensive, multidisciplinary approach to diagnosis and management, incorporating genetic testing, advanced imaging, and personalised treatment strategies to improve patient outcomes.

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