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Case Report

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A Rare Case of Testicular Leiomyosarcoma with a Four-Year Latency Before Pulmonary Metastasis: A Case Report

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Abstract

Introduction

Leiomyosarcoma (LMS) is a rare, aggressive smooth muscle malignancy that can metastasize the lungs. Testicular LMS is particularly uncommon, therefore, this case is unique due to its latency period before metastatic recurrence. Recurrence of LMS is usually within months to a year and here we present a case of a recurrence four years after diagnosis, followed by an integrative approach to care that included conventional and naturopathic oncology treatment.

Case Presentation

A 49-year-old Syrian male with a history of testicular LMS, initially treated in 2019 at NMC hospital in Abu Dhabi developed bilateral pulmonary nodules that presented as shortness of breath. He came to Burjeel Cancer Institute (BCI) for evaluation in August 2023 on self-referral and underwent biopsy and scanning which confirmed metastatic recurrence of the original testicular LMS, prompting the initiation of conventional treatment consisting of chemotherapy and then surgery. When his insurance coverage stopped, he started working with naturopathic oncology in combination with conventional therapies to help reduce side effects and prevent further progression.

Results and Discussion

This case presents a rare instance of testicular LMS with metastatic recurrence 4 years after initial surgical treatment, highlighting the potential for prolonged tumor dormancy. Most LMS recurrences occur within a few years, making this delayed metastasis an unusual and clinically significant event. The extended latency raises important considerations about tumor dormancy mechanisms, including immune evasion, dormant tumor stem cell microenvironmental changes, and circulating tumor cells. While dormancy markers have been identified in other cancers, their role in LMS remains unexplored. This gap underscores the need for further research into specific biomarkers that could guide risk stratification and inform surveillance protocols. Additionally, the integration of naturopathic oncology in this case draws attention to its potential immunomodulatory and anti-angiogenic effects, suggesting a possible role in prolonging dormancy or preventing recurrence. Although limited literature on naturopathic oncology care is available, the role of this modality in cancer managements warrants further investigation with naturopathy being part of an integrative oncology plan as part of comprehensive, long-term management strategy.

This case emphasizes the nature of LMS recurrence and supports the consideration of long-term follow-up guidelines, as well as exploration of integrative and naturopathic oncology therapies to enhance outcomes in patients with soft tissue sarcomas.

Keywords: Testicular Leiomyosarcoma, Pulmonary metastasis, Smooth muscle malignancy, Testicular cancer, Naturopathic oncology, Case report

1. Background

Leiomyosarcoma (LMS) is a rare and aggressive malignancy arising from smooth muscle cells, most commonly affecting the uterus and soft tissues, with less frequent involvement of the genitourinary tract, including the testis [1]. Testicular LMS

is exceedingly rare, constituting a small fraction of testicular malignancies, given that sarcomas account for only 1% of all malignant testicular lesions [2]. Despite its rarity, testicular LMS poses a significant risk of metastasis, most commonly to the lungs, liver, and lymph nodes [3]. Pulmonary metastases, the most frequent distant site of involvement, are often detected incidentally on imaging or present with symptoms such as dyspnea, cough, and chest discomfort [4].

The metastatic spread of LMS to the lungs primarily occurs via hematogenous dissemination, attributed to the tumor's increased likelihood for vascular invasion [5]. Prognosis in metastatic LMS is generally poor, with survival rates dependent on tumor burden, response to therapy, and the feasibility of surgical resection [6]. For soft tissue sarcomas, including LMS, the five-year survival rate is significantly higher for localized disease compared to metastatic cases, underscoring the aggressive nature of disseminated LMS [7]. Current treatment strategies include systemic chemotherapy, typically incorporating doxorubicin, ifosfamide, and mesna (AIM regimen)- targeted therapies based on molecular profiling, and surgical metastasectomy in select cases where complete resection is possible [8–11].

The underlying pathophysiology of LMS involves multiple genetic and molecular alterations, including recurrent copy number changes and mutations in tumor suppressor genes such as *TP53*, *RB1* and *PTEN* [12]. Immunohistochemical markers useful in LMS diagnosis include smooth muscle actin, desmin, and h-caldesmon, although none of these markers are entirely specific for LMS, necessitating histopathological confirmation [12]. Distinguishing testicular LMS from other testicular malignancies, such as germ cell tumors or lymphomas, is critical, as germ cell tumors typically exhibit more homogeneous imaging characteristics, whereas LMS often appears as a heterogeneous mass with high vascularity and a propensity for spermatic cord invasion rather than retroperitoneal lymph node involvement [13].

Several risk factors have been implicated in the development of LMS, including prior radiation therapy to the pelvic region has been linked to an increased risk of LMS in the testicles [14]. While research into environmental risk factors remains inconclusive, some studies have proposed potential associations with certain chemical exposures [15].

Given the aggressive nature and metastatic potential of testicular LMS, early recognition and multidisciplinary management are essential in optimizing patient outcomes. Prognostic factors such as tumor size, testis invasion, lymphovascular invasion, and tumor histology play a critical role in guiding risk-adapted treatment approaches [16]. This case report highlights the clinical course, histopathological findings, and therapeutic challenges associated with a patient diagnosed with metastatic testicular LMS, emphasizing the complexities of disease progression and management.

2. Case Description

A 49-year-old Syrian male with a history of left testicular LMS presented to Burjeel Cancer Institute in July 2023. He had travelled for Hajj and upon return complained of significant cough sputum and dyspnoea. His past medical history was significant for hyperlipidemia, chronic reflux and he had a smoking history of 15 pack-years.

As per his previous history, the testicular LMS was diagnosed and treated via left orchiectomy and followed by systemic chemotherapy (AIM) doxorubicin and ifosfamide in 2019 at a local hospital in Abu Dhabi. Due to being treated at another hospital previously, detailed records are missing before 2023. See Table **??** for the timeline.

Table 1: Timeline of Events.

2019	2023	2024	2025
LMS left orchiectomy. Doxorubicin Ifosfamide (AIM)	July PET recurrence	January SBRT 50Gy completed	January – March 2025 PET Stable disease with naturopathic oncology
	August biopsy Doxorubicin and ifosfamide started	April PET stable disease	
	December VATS surgery and started SBRT 50Gy in 5 fractions	August PET recurrence, Gemcitabine Docetaxel, naturopathic oncology started	
		Oct 2025 chemo stopped naturopathic oncology continued	

Initial Radiological findings: BCI Medical oncology team ordered PET scan on July 20, 2023 (Figure 1a), which confirmed

multiple discrete nodules in both upper and right lower lobes. The anterior segment of right upper lobe expressed mild Fluorodeoxyglucose (FDG) uptake, 1.96 Standardized Uptake Value (SUV) Max, currently measuring 2 x 2.5 cm (compared to 3.5 x 3.0 cm) and smaller non-FDG bilateral pulmonary nodules (not less than five) depicted, largest measuring 6.7 x 9.2 mm (compared to 13 x 10 mm) in the posterior segment of left upper lobe. There was no radiographic evidence of pleural effusion or pneumothorax. There were few FDG avid mediastinal lymph nodes noted, namely right hilar and parabronchial stations, largest measuring 10 x 13 mm in anteroposterior (AP) and transverse (TS) dimensions, SUV Max of 3.50, without evidence of mediastinal lymphadenopathy or abnormalities in the visualized bones and upper abdominal organs.

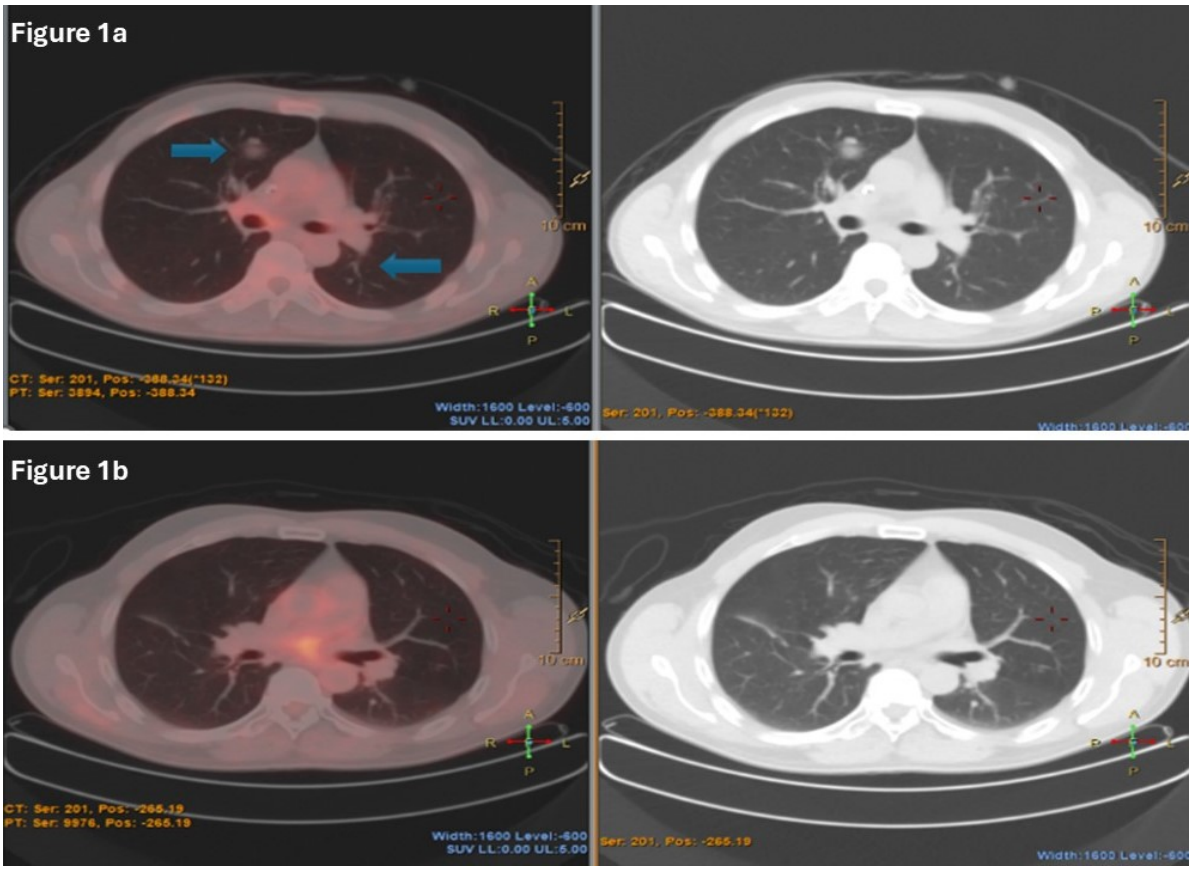

Figure 1: (a) PET-CT 2023 (Top) showing multiple discrete nodules in both upper and right lower lobes. (b) PET-CT 2024 after treatment (bottom) showing treatment response.

Immunohistochemistry findings: A right lung core biopsy on August 28, 2023, confirmed metastatic LMS, with immunohistochemistry (IHC) findings showing nuclear positivity for calponin (positive for smooth muscle marker in LMS) and negativity for Cytokeratin 20 (CK20), Cytokeratin Cocktail AE1/AE3 (CKAE1/3), Activin receptor-like kinase 1 (ALK1), Cytokeratin 7 (CK7), and Myoblast determination protein 1 (MyoD1).These IHC details are used to confirm the cell and protein markers that distinguish LMS from benign and other types of tumors including Rhabdomyosarcoma, or a tumor that does not arise from mesenchymal (smooth muscle) origin such as epithelial tissue marker expression found in lung cancer (adenocarcinoma). The biopsied LMS lung tumour cells were negative for myogenin, which ruled out rhabdomyosarcoma, and retained Interactor 1 (INI1) nuclear staining which rules in LMS. Due to insufficient tissue, the smooth muscle markers caldesmon and Cam 5.2 could not be interpreted.

Treatment regimen: The patient subsequently started treatment and completed 4 cycles of doxorubicin and ifosfamide. On December 14, 2023, the patient underwent a right video-assisted thoracoscopic surgery (VATS) with open pulmonary mastectomy. The patient received Stereotactic Body Radiation Therapy (SBRT) to the right upper lobe, right lower lobe, left upper lobe (2 lesions), a total of 50Gy in 5 fractions completed on Jan 26th, 2024.

Radiological findings after treatment: A PET scan on April 19th, 2024 (Figure 1b), reported few (not more than three) bilateral pulmonary nodules depicted without expressing FDG avidity, largest sub-pleural in the anterior segment of right upper lobe, measuring 5 mm in maximum dimension. Regression of the previously depicted non FDG pulmonary nodule in the posterior segment of left upper lobe measuring 5.2mm (compared to 6.7 x 9.2 mm). The other examined lung parenchyma was unremarkable with no evidence of FDG avid mass lesions or sizable nodules. No radiographic evidence of pleural effusion or pneumothorax was observed. Diffuse mild FDG uptake was noted in right upper chest walls, which could likely be post-operative changes. In addition, previously recurrent focal lesions, no less than 5 with low uptake SUV max 1.46 were

observed. Regression detected left upper pulmonary nodule and resolution of right hilar and parabronchial nodes, with T8 sclerotic foci SUV 5.67. No FDG avid lymphadenopathy was observed in the hilar, mediastinal, axillary, or internal mammary groups. The patient showed stable disease and excellent performance status, weight gain, and was generally doing very well without complications.

On May 6th 2024, the patient developed an acute localized skin and subcutaneous infection to his Port-A-Cath. It was thus removed the patient recovered without complications with diclofenac potassium 50mg (NSAID) and paracetamol/acetaminophen 500mg

LMS Recurrence: A PET scan on August 6th 2024 (Figure 2a), revealed evidence of FDG-avid newly developed lesions. On August 20th, 2024, the patient was started on second line treatment with docetaxel and gemcitabine chemotherapy.

Naturopathic Oncology Plan: The patient self-referred to the naturopathic oncology clinic for assessment on August 29th, 2024. No abnormal findings were present with physical examination aside from observed surgical scar. Baseline lab results dated September 23-30, 2024, revealed Vit D3 deficiency (13.2ng/nl) normal G6PD (13.4 U/gHb) and elevated AST (60 U/L).

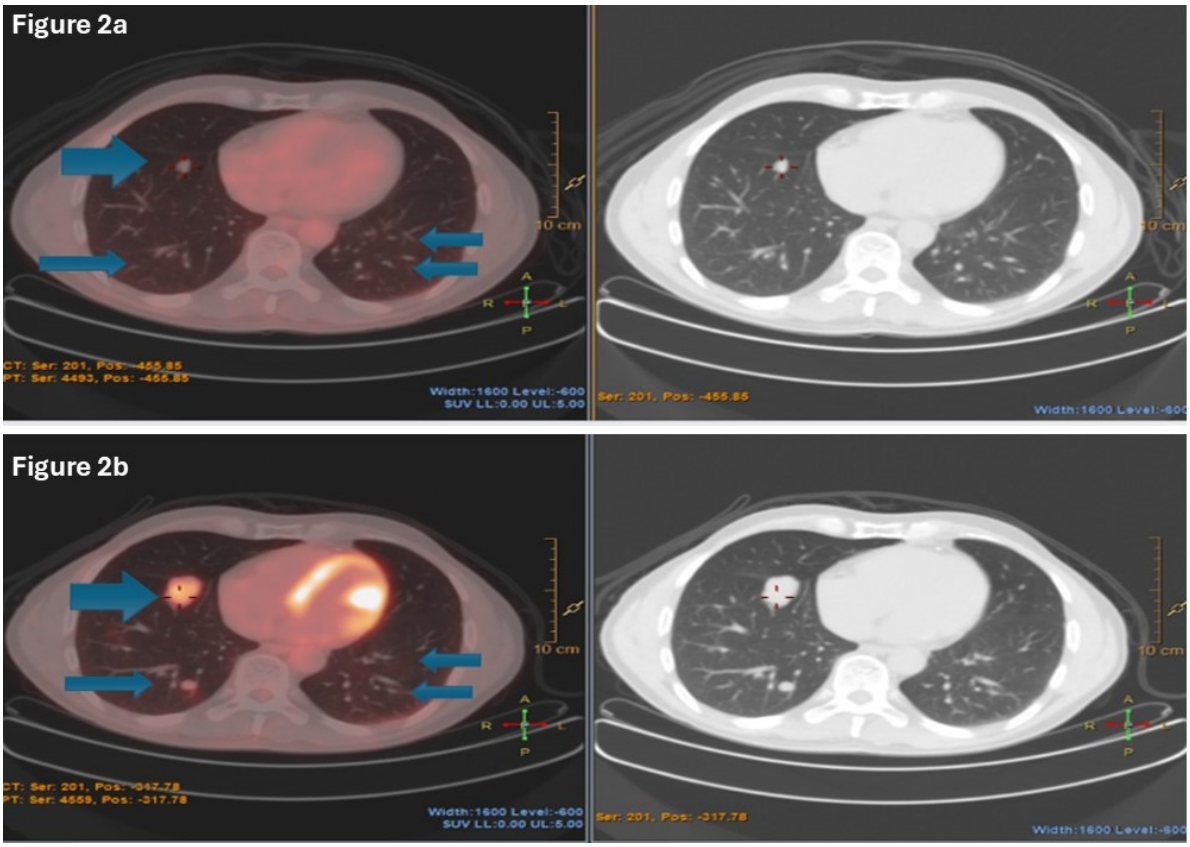

Figure 2: (a) PET-CT 2024 (Top) showing evidence of newly developed lesions. (b) PET-CT 2025 (bottom) indicating clear progression.

The naturopathic oncology plan focused on supporting chemotherapy, restoring metabolic and immune function, correcting nutritional deficiencies, reducing chronic inflammation, reducing the severity of chemotherapy induced adverse effects such as pain, fatigue, neuropathy, agranulocytosis, thrombocytopenia, stress, and the GI adverse effects of constipation, nausea, and mouth sores. The detailed prescribed supplement plan for metabolic and immune function included melatonin, vitamin D3, omega-3 (EPA from fish oil), honokiol extract (Magnolia officinalis), turmeric (Curcuma longa), zinc, black cumin seed oil (Nigella sativa), and boswellia AKBA (Boswellia serrata). The supportive care for reported adverse effects included dose-specified botanical extracts of reishi (Ganoderma lucidum), astragalus (Astragalus membranaceous), skullcap (Scutellaria baicaleinsis), probiotics, in in addition to detailed clinical nutrition and exercise prescription.

Integrative Standardized Chemotherapy and Naturopathic Plan: On September 11, 2024, following the first cycle of gemcitabine and docetaxel, the patient was admitted to the hospital due to chemotherapy induced agranulocytosis (thrombocytopenia and leukopenia), and Grade 3 GI adverse effects of nausea and diarrhea. He was treated with intravenous fluids, gastric protectants (pantoprazole), antiemetics (paracetamol, ondansetron), and thrombopoietic agents (romiplostim). On September 19, 2024, he was prescribed denosumab and ondansetron and continued chemotherapy with the gemcitabine and docetaxel. Additional medications, including dexamethasone, pegfilgrastim, diphenhydramine with the continuation of chemotherapy docetaxel, and gemcitabine, were added on September 30, 2024. He ran out of sick leave at work, lost his employment, his insurance coverage stopped and he discontinued chemotherapy due to cost.

From September 19, 2024 the patient was referred to receive high-dose intravenous Ascorbate (IVAscorbate) 75 grams twice weekly. On January 20, 2025, mistletoe subcutaneous injection immunotherapy (Helixor A, Series 1 and 2) was also added. In addition, the patient was also taking specific botanical extracts at prescribed doses, all for metabolic and immune signaling. The patient was compliant and responded well as evidenced by his ability to return to work in November 2024, his chemo-induced agranulocytosis returned to normal, and his re-gain of lean muscle mass. He stopped IV Ascorbate due to cost in January 2025. The patient had remained stable, and on a follow up consultation February 5, 2025, he reported some fatigue. As a result, integrative treatment regimen was intensified, including resuming IV Ascorbate.
The patient returned for consultation in October 10th, 2025, with complaints of mild weight loss (4kg over the last 4 months), intermittent Barretts' esophagitis and gastritis, and fatigue in the morning, all of which he also attributed to his work-related stress. He reported that he remained on the naturopathic oncology protocol as given to him in August 2024. His nutrition and exercise remained the same and the Oct 13th bloodwork (CBC and CMP), urine and stool testing completed was normal aside from elevated iron (161 ug/dL) and low potassium (3.4mmol/L). His 25-OH Vit D3 was 56 ng/mL, fecal Calprotectin was normal (30ug/g), Ferritin was normal (203ug/L) and Absolute Neutrophil to Lymphocyte Ratio (ANLR) was 2.58. Cardiac stress was ruled out from gastritis with the Troponin-T HS results being normal (6.2-8.5ng/L). The cardiac, pulmonary and abdominal physical examination was normal/unremarkable. He was referred for PET scan for follow up in oncology. The October 2025 (Figure 2b) PET-CT indicated progression of tumor deposits in the lungs bilaterally. At this development of progression the oncologist prescribed Pazopanib, a Tyrosine Kinase Inhibitor, which the patient subsequently declined citing side effects and not being able to take time off and risk losing his job again. He completed a Naturopathic oncology consultation which resulted in strong encouragement of the use of the prescribed Pazopanib with additional strategic multi-target cell signal and DNA repair inhibition on known LMS targets (See Table 2) including Poly-ADP-Ribose Polymerase (PARP), vascular endothelial growth factor (VEGF), altered glycolysis (GLUT1, HIF1alpha), Tyrosine Kinase Inhibition (TKI) and Histone De-Acetylase (HDAC) inhibition. This translated to the therapeutic dosing of butyrate, resveratrol, quercetin, luteolin, curcumin, berberine, and sulforaphane [17–23], see Table 2. Additive to Pazopanib effects the recommendation was made to include Melatonin (VEGF inhibition) and Zinc (PARP inhibition). IV Ascorbate 75 gam infusions twice weekly and Helixor M (mistletoe) were resumed. Past exposure to Doxorubicin required long term use of CoQ10 for cardiac muscle health and that remained at 300mg twice daily. De-glycyrrhizinated Licorice (DGL) lozenges were prescribed for the chronic gastritis and esophageal reflux.

Table 2: LMS Targets and their Natural Agents [17–23].

Tumor Target	**Natural Agent**
Poly-ADP-Ribose Polymerase (PARP)	Zinc [17]
Vascular endothelial growth factor (VEGF)	Melatonin [18]
Altered Glycolysis	IV Ascorbate [19]
Tyrosine Kinase Inhibition (TKI)	Curcumin [19, 20]
Histone De-Acetylase (HDAC) inhibition	Sulforaphane, EGCG, Resveratrol, Butyrate, Curcumin, Quercetin, Luteolin [21, 22]
mTOR inhibition via PI3K/AKT or activation of AMPK to inhibit mTORC1 or ATP-competitive inhibition	Curcumin, Resveratrol, Quercetin, EGCG, Berberine, Honokiol [23]

At the time of case report submission, the ECOG score of the patient is 0. He is still alive, working and exercising with normal quality of life and functionality.

3. Discussion

This case presents a rare instance of testicular LMS with a 4-year disease-free interval before metastatic recurrence in the lungs. Such a prolonged dormancy period is uncommon in soft tissue sarcomas. Most metastasis in LMS occurs within the year of initial treatment. The long latency period in this case suggests potential metastatic drivers and mechanisms, including immune evasion, vascularization processes, tumor metabolism and micro-environmental changes, and circulating tumor cells. Even after the primary tumor is surgically removed, dormant cancer cells can become active again and lead to metastases years later, emphasizing the importance of long-term follow-up [24]. Given the later recurrence this case highlights the need for reconsidering long-term follow-up guidelines for LMS patients. Tumor dormancy occurs when cancer cells enter a state of cell cycle arrest, halting division while remaining viable. This is often triggered by factors such as an unfavorable microenvironment, limited blood supply, immune system pressure, and ongoing treatment pressure, thereby allowing the cells to exist undetected by the immune cells before potential reactivation events and signals [24].
Circulating tumor cells (CTCs) can serve as indicators of tumor dormancy and early recurrence in blood circulation. Research has identified early markers of recurrence in other tissue types: urokinase plasminogen activator receptor and integrin subunit beta-1 as dormancy markers in epithelial cell adhesion molecule-negative CTCs, which exhibit stem cell-like properties that

enhance brain metastasis. These CTCs also show increased expression of genes associated with DNA repair and blood brain barrier permeability, which may contribute to their survival and metastatic potential [25].

Additionally, the activation of mTOR complex 2 and reduced mTORC1 signaling have been linked to the long-term dormancy of disseminated tumor cells (DTCs) in the bone marrow [25]. These findings underscore the role of CTC biomarkers in understanding tumor dormancy and guiding personalized cancer treatments [25]. However, these dormancy markers have been primarily studied in the context of brain metastases and bone marrow DTCs, with no established literature specifically addressing the role in LMS. This gap highlights the need for research into the dormancy mechanisms of LMS and the identification of reliable monitoring markers for this rare malignancy.

Understanding dormancy markers in LMS could have significant clinical implications. If reliable biomarkers are identified, they could guide treatment and surveillance strategies, helping to determine targets for treatment and identify risk for recurrence. More importantly, they could inform the timing of treatments such as targeted therapies to disrupt tumor cell replication signaling dormancy pathways before reactivation occurs. Identifying these markers could lead to proactive treatment strategies, ultimately improving patient outcomes and increasing survivorship and time to recurrence with more effective precision treatments [26–29].

Mistletoe subcutaneous injection therapy (Helixor, Iscador) has gained attention in oncology for its evidence in reducing fatigue and for its immune modulating properties when used during conventional oncology treatment. It is used safely for over 80 years alongside conventional treatment in some European countries for fatigue reduction.

In this case, mistletoe was introduced after the recurrence of disease keeping mistletoe's possible role in recurrence prevention. The cytotoxic effects of mistletoe extract result from its ability to interfere with protein synthesis, induce cell cycle arrest, and promote apoptosis, leading to direct tumor cell destruction [30]. Mistletoe extract has demonstrated anti-angiogenic properties, which may help prevent tumor growth and metastatic spread by inhibiting the formation of new blood vessels. Furthermore, its immune-modulating effects may enhance the body's ability to recognize and suppress tumor cells, potentially reducing the risk of recurrence [30].

While mistletoe has primarily been used to support cancer treatment and symptom management, its mechanisms suggest that it may also have a preventive role by prolonging tumor dormancy and reducing the likelihood of reactivation. Future studies can build on the established data to explore optimal dosing, timing and synergy with conventional therapies in neo-adjuvant treatment and recurrence prevention. Establishing evidence on mistletoe's ability to affect cancer recurrence will contribute to comprehensive long-term integrative treatment strategies and possibly better patient outcomes.

This case raises critical questions: What are the metabolic and immune drivers of recurrence in LMS? Could specific immune or metabolic biomarkers help identify patients at risk for delayed metastasis? How might naturopathic oncology therapies impact cancer progression if used at the time of diagnosis with conventional treatment? This case highlights the unpredictable nature of LMS recurrence and the necessity for prolonged vigilance. Future research should focus on refining surveillance protocols and sounding out the benefits of integrative care and specifically naturopathic oncology in all stages of cancer care.

4. Conclusion

This case highlights the unpredictable nature of testicular LMS recurrence, with a rare 4-year latency period before metastatic progression. It highlights the importance of long-term surveillance strategies. Understanding the mechanisms of tumor dormancy, CTCs, and immune evasion could provide valuable insights into predicting and preventing LMS reactivation.

While biomarkers for tumor dormancy have been studied in brain and bone marrow metastases, no established markers currently exist for LMS. Identifying specific dormancy markers could enhance risk stratification, inform surveillance strategies, and allow for early intervention before metastatic resurgence. Future research should prioritize biomarker discovery, predictive modeling, and personalized long-term monitoring protocols for LMS patients.

Ultimately, this case emphasizes the need for proactive approaches to LMS management. By expanding research on tumor dormancy, refining surveillance protocols, and integrating targeted therapies, clinicians may better address the long-term challenges of LMS recurrence and enhance patient care.

5. Declarations

Ethics Approval and Consent to Participate

Ethics approval and written informed consent were obtained.

Consent for Publication

Written informed consent for publication was obtained from the patient.

Data Availability Statement

Not applicable.

Conflicts of Interest

The authors declare no competing interests.

Funding

The authors declare no funding was provided.

Author Contributions

HK and MG collected the clinical data and wrote the manuscript.

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