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Anatomy of Multimorbidity: A GIST Case Study

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ABSTRACT

The anatomy of multimorbidity refers to the composition and patterns of coexisting chronic conditions within an individual, often involving multiple body systems with complex interactions and management challenges.[1-4]

This case study highlights a 74 years old age male with multimorbidity developing starting 1990 – smoker in college, nonalcoholic drinker, s/p cholecystectomy; fatty liver, cysts, proceeding to hepatomegaly; multinodular goiter; 1st degree AV block, cardiomegaly, LV EF 71%, aortic valve sclerosis, hypertension urgency, dyslipidemia, non-insulin dependent diabetes, non-specific interstitial lung disease, benign prostatic hypertrophy, benign positional paroxysmal vertigo, kidney stones renal cysts, chronic kidney disease, sleep apnea, diffuse idiopathic skeletal hyperostosis, spondylosis, arthritis; admissions for pneumonia/ bronchitis; skeletal abnormalities, spondylosis, arthritis; venous insufficiency, chronic peripheral edema; incompetent right sapheno-femoral venous junction; chronic venous stasis and bilateral leg edema with cellulitis. This 2025, he was diagnosed with GIST (gastrointestinal stromal tumor).

Keywords: Multimorbidity; Cancer; GIST

INTRODUCTION

Multimorbidity is most commonly defined as the presence of two or more chronic long-term conditions in the same person, including physical, mental health, sensory impairments, and symptom complexes such as frailty or chronic pain. Complex multimorbidity is often defined as having three or more conditions affecting three or more different body systems, highlighting the complexity of care required.[1-3]

The anatomy of multimorbidity refers to the composition and patterns of coexisting chronic conditions within an individual, often involving multiple body systems with complex interactions and management challenges. Key aspects include:

- **Body system groupings:** Chronic conditions tend to cluster into groups based on the body systems affected. A study classified multimorbid conditions into nine clusters: cardiovascular; musculoskeletal and pain; respiratory and skin; digestive; excretory or urinary; visual; mental health; cancer; and accidents/injuries. These clusters show how conditions co-occur and potentially interact.[4]
- **Mental-physical multimorbidity:** The combination of mental and physical health conditions forms a distinct pattern of complexity, often more prevalent and occurring at younger ages in deprived populations. This type of multimorbidity may increase treatment burden and complicate management beyond what can be captured by counting affected body systems alone.[1]
- **Pathophysiology and mechanisms:** Multimorbidity development is influenced by ageing-related changes (genomic instability, inflammation, cellular senescence), socioeconomic and behavioral factors, and medication effects. These factors contribute to both concordant multimorbidity (conditions with shared pathophysiology, e.g., multiple cardiovascular diseases) and discordant multimorbidity (conditions with unrelated mechanisms, e.g., COPD and depression).[2]
- **Clinical implications:** Understanding the anatomy of multimorbidity—how different conditions cluster and interact across body systems—helps in healthcare planning and tailoring treatment, given the increased complexity and polypharmacy that patients face. Interdisciplinary care might be necessary due to involvement of diverse specialists depending on the affected body systems.[3]

Multimorbidity is highly prevalent among people with cancer, particularly those living with and beyond cancer. The rate of multimorbidity in cancer survivors can be up to three times higher in all cancer survivor groups compared to non-cancer controls. Childhood cancer survivors also exhibit a higher prevalence of chronic multimorbidity compared to peers without cancer. Multimorbidity in cancer patients include the following key points:

- **Prevalence:** Multimorbidity is very common among cancer survivors. For instance, the prevalence of having at least one additional chronic condition (beyond cancer) ranges from 40–69%, while having two or more additional conditions ranges from 12–32%. Large studies show that while 46% of cancer survivors have 1-2 additional long-term conditions—similar to the general population—they are far more likely to have 3-4 or even 5+ co-occurring conditions.[5,6]
- **Influencing factors:** Age is also a significant factor, as older individuals are more prone to both cancer and multimorbidity. Shared risk factors such as obesity and biological mechanisms (e.g., insulin pathways linking diabetes and cancer) contribute to the co-occurrence. Multimorbidity is more common among those from ethnic minority groups and those with lower socioeconomic status. These factors are also linked to reduced access to care and additional barriers that further degrade outcomes and quality of life.[5-7]
- **Impact on Quality of Life and Care:** Cancer survivors with multimorbidity tend to have poorer quality of life than those without multimorbidity. The presence of multiple conditions complicates treatment plans, increases healthcare needs, and is associated with receiving less aggressive or non-

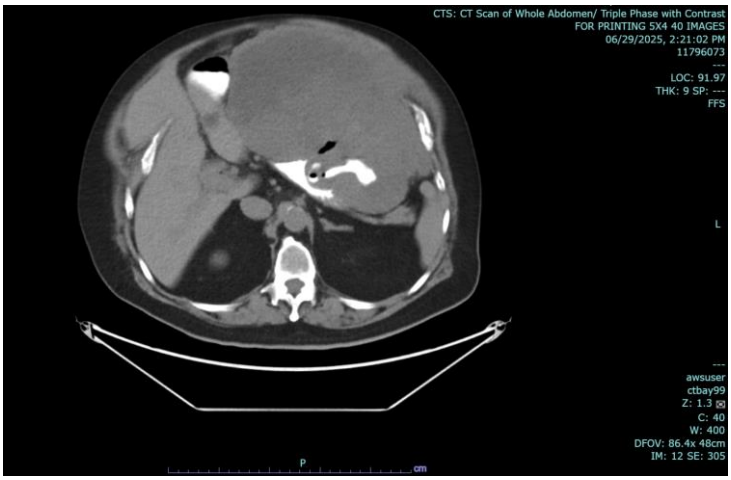
curative cancer treatments. The complexity of managing multiple conditions also highlights the limitations of a "single-disease" care model.[5,6,8]

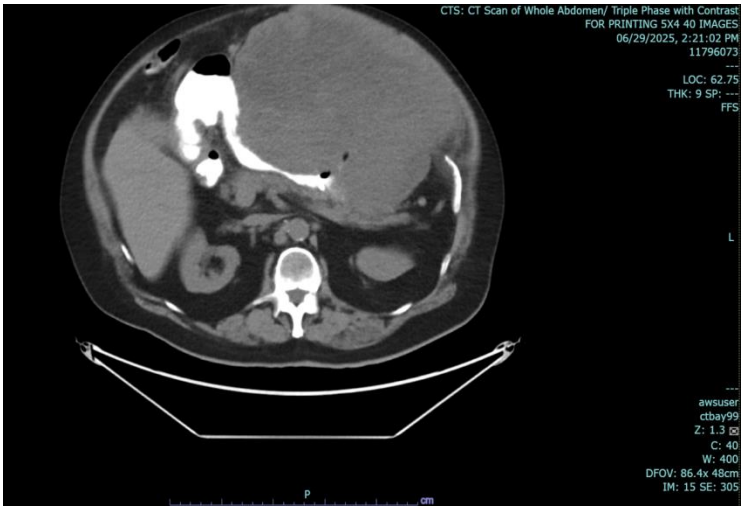
- **Most Common Co-Existing Conditions:** The chronic conditions most frequently seen alongside cancer are hypertension, heart conditions (including heart failure), depression, chronic obstructive pulmonary disease (COPD), and diabetes. After cancer diagnosis, new conditions like congestive heart failure, chronic pain, chronic fatigue, and mental health disorders like anxiety commonly develop.[5,6,9]
- **Varies by Cancer Type:** The patterns and types of comorbid conditions can differ by cancer site. For example, breast cancer survivors most commonly report hypertension (~36.7%) and chronic pain (~18.3%); prostate cancer survivors often have hypertension (~44%) and heart disease; colorectal cancer survivors frequently have hypertension (~43%) and arthritis (~32%); liver cancer has higher alcohol-related diseases, and cancers of stomach, esophagus, multiply myeloma have highest prevalence of anemia.[5,6,9]
- **Role of Cancer and Its Treatments:** Some comorbidities may develop or worsen after a cancer diagnosis, potentially as a result of cancer treatments (e.g., chemotherapy toxicity leading to heart failure) or the physical and psychological stress of cancer and survivorship. Increased healthcare contact can also lead to greater detection of pre-existing conditions.

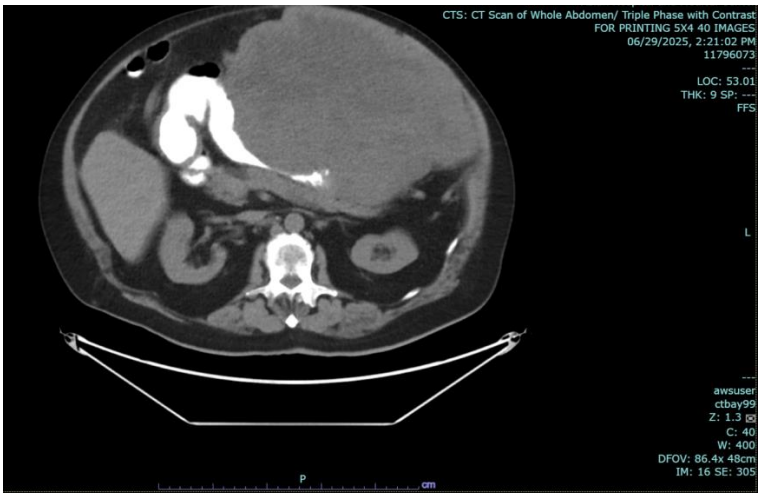
CASE STUDY

This case study highlights a 74 years old age male with the following medical history:
1990 - s/p cholecystectomy, s/p appendectomy, smoker in college; 2010 - fatty liver; 2013 - liver cysts; 2015 - multinodular goiter, 1st degree AV block, cardiomegaly, LV EF 71%, aortic valve sclerosis, hypertension urgency, dyslipidemia, non-insulin dependent diabetes, non-specific interstitial lung disease, benign prostatic hypertrophy, benign positional paroxysmal vertigo, kidney stones, sleep apnea; 2018 - diffuse idiopathic skeletal hyperostosis, moderate hepatic steatosis, renal cysts; 2019 – pneumonia/ bronchitis hospital admission; 2023 - hepatomegaly with persistent fatty change, left liver lobe cyst 1.6 x 1.1 x 1.3 cm, lumbosacral spine MRI – L3-L5 posterior intrusional spur & diffuse disc bulge with posterior annular tear with resultant moderate narrowing of bilateral neural foramina abutting bilateral traversing nerves, L2-L3 to L5-S1 disc desiccation, spondylosis, arthritis, kidney calculus, venous insufficiency, chronic peripheral edema; incompetent right saphenofemoral venous junction; chronic venous stasis, bilateral leg edema, cellulitis.

In June 2025, he had left pleural effusion (chest x-ray), with an abdominal CT Scan showing exophytic lobulated gastric mass with central hypodense areas (likely necrosis) arising from fundus and proximal body of stomach, 16.9 x 25 x 17.8 cm exerting severe mass effect on remaining stomach pancreas, left hepatic lobes transverse colon, abuts left hemidiaphragm and distends anterior abdominal wall, CEA 1.01 ng/ml, CA 19-9 7.6 iu/ml, AFB 1.93 ng/ml, now also with chronic kidney disease**.** Gastroscopy with endoscopic UTS – 129.17 x 97.11 mm hypoechoic mass with lobulations at gastric wall adjacent to liver, with some bleeding. Gastric mass biopsy July 2025 showed GIST (gastrointestinal stromal tumor), spindle cell type, mitotic rate 4 per 5 mm sq, low grade, CD34+, CD117+, Desmin-, DOG1+, HER-, S100-, Ki67-, 21-30% proliferative index, no loss of nuclear expression of MMR proteins. He underwent blood transfusion. He has osteopenia/ osteoporosis, nociceptive visceral pain.







He started imatinib 7 July-16 July 2025, at 600 mg a day, stopped when he got admitted for infection (cellulitis) and anemia. He resumed imatinib 400 mg a day 23 July up to 12 September, when he was admitted with dyspnea, progressing leg erythema and enlargement. He was managed as a case of bilateral pleural effusion

noted without malignant cells, acute pulmonary congestion, paroxysmal atrial fibrillation in rapid ventricular response, recurrent moderate skin and soft tissue infection of the bilateral lower extremities, considering sepsis, impending acute renal failure, multifactorial anemia and hypoalbuminemia, occult gastrointestinal blood loss, GIST, bronchial asthma, metabolic syndrome. Imatinib was resumed after 13 days. CTScan showed regressing tumor mass. Patient recovered and cleared for discharge with continuing medical management on an out-patient basis.

DISCUSSION

Multimorbidity, the presence of two or more chronic health conditions in addition to cancer, is a significant factor in cancer care, impacting patient outcomes and treatment decisions. It is common among cancer patients and can affect their quality of life, treatment tolerance, and survival rates. Cancer patients would also have other long-term health conditions, such as: cardiovascular diseases (heart disease, stroke, high blood pressure, high cholesterol), respiratory conditions (asthma, COPD), metabolic disorders (diabetes, azotemia), mental health conditions (depression, anxiety), and other chronic illnesses (arthritis, chronic pain).

We show case herewith a 74 years old age male with multimorbidity developing since 1990 – smoker in college, nonalcoholic drinker, s/p cholecystectomy, fatty liver, cysts, proceeding to hepatomegaly, multinodular goiter, 1st degree AV block, cardiomegaly, LV EF 71%, aortic valve sclerosis, hypertension urgency, dyslipidemia, non-insulin dependent diabetes, non-specific interstitial lung disease, benign prostatic hypertrophy, benign positional paroxysmal vertigo, kidney stones renal cysts, now with chronic kidney disease, sleep apnea, diffuse idiopathic skeletal hyperostosis, spondylosis, arthritis, admissions for pneumonia/ bronchitis, cellulitis, skeletal abnormalities, spondylosis, arthritis, venous insufficiency, chronic peripheral edema, incompetent right sapheno-femoral venous junction, chronic venous stasis, bilateral leg edema up to current. In June 2025, he was diagnosed with GIST.

Gastrointestinal stromal tumors (GISTs) are considered rare tumors, accounting for less than 1% of all gastrointestinal tumors. Global incidence is estimated at about 10 to 15 cases per million people per year (approximately 1.5 per 100,000 population). Despite their rarity, GISTs are the most common mesenchymal tumors of the gastrointestinal tract, representing around 80% of gastrointestinal non-epithelial tumors and about 5% of all sarcomas. The most frequent primary site for GIST is the stomach (about 63% of cases), followed by the small intestine (around 30).[10-12]

GIST frequently coexists with other primary tumors, especially gastric adenocarcinoma, lymphoma, prostate, breast, kidney, and lung cancers. The coexistence of GIST with other malignancies complicates diagnosis and management, sometimes leading to under diagnosis preoperatively, which impacts therapeutic planning.[13]

GIST patients commonly have other chronic conditions typical of an older population, such as diabetes, cerebrovascular disease, ischemic heart disease, chronic lung disease, and congestive heart failure. These comorbidities add complexity to treatment decisions, especially since GIST primarily affects older adults with a median diagnosis age around 64–65 years.[13-15]

GIST develops via mutations—most commonly in the KIT or PDGFRA genes—but in patients with multimorbidity, its progression and treatment outcomes are substantially affected by coexisting chronic conditions, aging, and frailty. Multimorbid patients are frequently older, which may further increase biological heterogeneity in GIST development and resistance mechanisms (e.g., additional mutations under therapy). GIST in a multimorbid patient develops through typical oncogenic mutations but is deeply influenced in progression, risk, and therapeutic approaches by the patient's coexisting medical conditions, age-related frailty, and the likelihood of adverse treatment effects. Comorbidities may influence certain GIST molecular features mainly through association with syndromic or hereditary conditions but do not typically cause new mutations or directly alter the driver mutations (KIT, PDGFRA) found in sporadic cases. Clinical comorbidities such as diabetes or cardiac disease do not independently cause new GIST mutations but may increase host vulnerability and alter response to systemic therapies through organ dysfunction or drug metabolism. Comorbidities are most likely to change GIST molecular features when they arise as part of syndromic/hereditary contexts, but ordinary chronic diseases do not directly alter driver mutations of sporadic GIST. Treatment complexity may be increased, but the core tumor biology for sporadic GIST remains centered on KIT/PDGFRA or wild-type status. [16-21]

Comorbidities significantly influence treatment choices for patients with GIST in several key ways. Comorbidities, along with disability and frailty, can affect the patient's ability to tolerate systemic treatments like tyrosine kinase inhibitors (e.g., imatinib). Older patients with multiple comorbidities may experience more adverse effects such as edema, anemia, ocular toxicities, and fluid retention, requiring close monitoring and possible dose adjustments or reductions to balance efficacy and safety.[16]

Surgical resection is the standard curative treatment for localized GIST. However, in patients with significant comorbidities—such as cardiovascular or pulmonary diseases—surgery may be contraindicated or carry higher risks. In such cases, less invasive options like endoscopic ultrasound-guided alcohol ablation may be considered, particularly if surgery poses excessive risk due to accompanying medical conditions.[10,12] Surgical eligibility for GIST includes tumors ≥2 cm that are technically resectable with acceptable morbidity, patients with symptomatic lesions, and those in suitable health status. Multidisciplinary evaluation is recommended to tailor the approach, especially for large, borderline resectable, or metastatic tumors.[23-26]

Studies show that older GIST patients with more comorbidities are less likely to receive adjuvant imatinib therapy after surgery, despite clinical indications. This may be due to concerns about comorbidity-related complications, toxicity, and overall life expectancy, leading to differing treatment approaches compared to younger, healthier patients.[13,23,24] In GIST patients with multimorbidity, imatinib remains the first-line systemic therapy and is generally well tolerated, but comorbidities require careful management to optimize safety and effectiveness.[16,23,27,28] Neoadjuvant imatinib therapy for GIST is primarily used to shrink large or anatomically challenging tumors before surgery, improving surgical outcomes and preserving organ function.[28-30] Large GISTs (commonly ≥10 cm) or tumors in difficult locations (e.g., gastroesophageal junction, duodenum, rectum) where upfront surgery risks significant morbidity. Cases where tumor shrinkage may enable less extensive or

organ-preserving surgery and reduce risk of tumor rupture. Standard dose on imatinib is 400 mg daily orally; higher dose of 800 mg daily may be used for KIT exon 9 mutations due lower sensitivity at 400 mg. Typically 3 to 6 months is recommended to reach maximal tumor response before surgery. Some studies suggest treatment can be extended up to 9–12 months if the tumor continues to shrink without progression or resistance. Surgery is planned at the point of best response, ideally before secondary resistance develops. Neoadjuvant imatinib achieves significant tumor shrinkage in 60–70% of patients, facilitating high rates of complete (R0) resection (often >85–90%). It is effective in improving progression-free and overall survival when used as part of combined modality therapy. Early response can be evaluated by PET scan within 2–4 weeks. CT or MRI imaging is used during therapy to assess tumor size and resectability. Adjuvant imatinib is generally recommended after surgery in patients with high-risk features, including those who received neoadjuvant therapy, though optimal duration and sequencing remain areas of ongoing research. Imatinib's safety profile is favorable; severe adverse effects are uncommon and mostly occur early in treatment. The common toxicities include edema, anemia, rash, and ocular effects. These can be more pronounced or challenging to manage in multimorbid or elderly patients, often necessitating close monitoring and dose adjustments.[16,22-25] Studies show similar progression-free survival (PFS) and disease-specific survival (DSS) between older patients (including those over 70 or 75 years) with multimorbidity and younger, healthier patients treated with imatinib. However, older patients tend to have shorter overall survival, partly due to other comorbid conditions. Multimorbid patients, especially elderly ones, frequently undergo dose reductions because of toxicity. Despite dose adjustments, efficacy typically remains comparable to younger patients. Regular assessment of comorbidities and organ function (cardiac, hepatic, renal) is crucial to anticipate and manage adverse effects. Multimorbidity, polypharmacy, and frailty increase risk for adverse drug reactions, underscoring the need for multidisciplinary care and personalized treatment planning. While progression-free survival (PFS) and overall survival (OS) with treatments like imatinib can be comparable between older and younger patients, the presence of comorbidities is associated with shorter OS and higher risk of disease recurrence. This highlights how comorbid conditions can indirectly influence prognosis by affecting treatment feasibility and tolerance.[13] Beyond tumor characteristics, treatment strategies must consider patient age, performance status (e.g., ECOG), life expectancy, and comorbidities to optimize outcomes and quality of life. Multidisciplinary decision-making is essential to balance treatment benefits and risks in the context of multimorbidity.[13,22,23] Maintaining TKI therapy even after progression may improve outcomes while alternative options are explored.

In patients with significant comorbidities, GIST can develop and progress at variable rates—often slower than aggressive cancers, but growth can accelerate, sometimes leading to acute complications like bleeding within months to a few years. GIST in patients with comorbid conditions grows at a variable rate, with tumor doubling often observed in 17–19 months, but can accelerate to less than 6 months in high-risk cases, with other health issues.

Imatinib markedly slows tumor doubling time in unresectable GIST, converting rapid tumor growth into prolonged disease stabilization for most patients as long as drug sensitivity is maintained. Without treatment, unresectable or metastatic GISTs may double in size in less than 6–12 months depending on mutation profile and tumor biology. Imatinib inhibits KIT and PDGFRA-driven cell proliferation, shifting many unresectable

GISTs into a state of minimal growth or even shrinkage—doubling time is extended to years or longer in responsive cases. With continuous imatinib, imaging studies report tumors entering a "non-proliferative state" where significant growth ceases; discontinuation of imatinib leads to rapid regrowth, confirming the drug's suppressive role on tumor kinetics. Around 65–70% of patients achieve partial response, and 15–20% remain stable on imatinib, with median response duration exceeding 2 years prior to emergence of resistance. Disease progression resumes only after development of secondary (acquired) resistance, with tumor doubling time returning to pre-treatment rates. Long-term imatinib therapy thus maintains slow tumor kinetics, prolongs time to progression, and is considered standard for unresectable GIST. [31-35]

Slower tumor shrinkage with imatinib is predicted by specific clinical and biological factors—namely poor performance status, non-KIT exon 11 mutations, high baseline neutrophil counts, high mitotic index, low albumin/hemoglobin, and non-spindle cell histology.[36] High baseline neutrophil count and low albumin/hemoglobin have independently predicted poorer shrinkage and progression-free survival in treated cohorts.[37] Tumor size and site impact shrinkage rates; larger, more centrally located, or metastatic tumors typically respond more slowly.[38] Patients with non-KIT exon 11 mutations, poor general condition, high mitotic index, and unfavorable laboratory values are most likely to experience slower tumor shrinkage on imatinib.[39]

In a patient with GIST and significant multimorbidity—including cardiovascular disease, infection, diabetes, azotemia (renal impairment), anemia, dyslipidemia, cellulitis, and electrolyte imbalance—treatment guidelines emphasize an individualized, multidisciplinary approach that balances effective cancer control with safe management of comorbid conditions, drawing primarily from the latest 2023 GEIS guidelines and relevant clinical evidence.[25] Careful evaluation and stabilization of comorbid conditions are essential before initiating and during GIST-specific therapy:

- Optimize cardiovascular status to reduce perioperative and pharmacotherapy risks (e.g., control hypertension, heart failure).
- TKIs like imatinib, sunitinib, and regorafenib can exacerbate hypertension, cause fluid retention, or increase cardiac events; therefore, cardiology involvement is advised.
- Monitor and manage azotemia carefully as renal impairment may affect drug metabolism and dosing. Imatinib Dose adjustments and close monitoring are required in patients with comorbidities, especially renal impairment (azotemia) and cardiovascular disease, due to possible toxicities such as edema, fluid retention, and anemia.
- Active infections such as cellulitis should be controlled prior to initiating immunomodulatory treatment, and vigilance for infections should be maintained during therapy.
- Diabetes and dyslipidemia management should be optimized, with consideration of potential TKI interactions affecting glucose and lipid metabolism.
- Anemia and electrolyte imbalance require correction to improve performance status and treatment tolerance and ongoing monitoring to minimize treatment interruptions and complications.
- Regular assessment for adverse effects and drug interactions is necessary given polypharmacy common in multimorbid patients.

- In patients with heavy comorbidity burden and limited functional reserve, treatment goals may shift toward symptom control and quality of life rather than aggressive interventions.

It must be said however that multimorbidity in GIST patients is strongly associated with worse prognosis due to increased risk of treatment complications, limitations in therapy selection, and overall frailty, particularly in the elderly, all of which negatively impact survival and recurrence rates. Older age and the presence of other chronic conditions (including secondary cancers) have been shown to negatively impact outcomes. Elderly and multimorbid GIST patients are less likely to undergo surgical resection or receive adjuvant therapy—even when their performance status is relatively preserved. Multimorbidity, especially when combined with advanced age and polypharmacy, raises the risk of adverse drug reactions and treatment interruptions. Even when treated with tyrosine kinase inhibitors (such as imatinib), frail or multimorbid patients experience a higher incidence of side effects that can lead to discontinuation of therapy and suboptimal disease control. Comorbidities are linked to a higher risk of disease recurrence and shorter overall survival in older GIST patients.

Overall, the optimal management of a GIST patient with extensive multimorbidity requires individualized treatment planning, prioritizing stabilization of comorbidities, careful use of surgery and TKIs like imatinib with dose adjustments and monitoring, and coordinated multidisciplinary care to maximize cancer control while minimizing risks. Comorbidities in GIST and similar other tumor-related patients influence treatment choices by affecting surgical candidacy, tolerance to systemic therapies, treatment intensity, and ultimately patient outcomes. Clinicians must carefully evaluate and manage these comorbidities to individualize treatment plans, especially in elderly or frail patients.

While multimorbidity is common across all cancer types, specific patterns of comorbid long-term conditions differ, reflecting both shared risk factors and cancer- or treatment-specific effects. This underscores the need for cancer-type tailored approaches to multimorbidity management in survivorship care. Multimorbidity in cancer patients is multifaceted, and significantly impacts both clinical decision-making and survivor well-being, requiring a coordinated and personalized approach to healthcare in this growing population. There is a need for standardized methods to measure multimorbidity in cancer populations, more comparative data on multimorbidity before and after a cancer diagnosis, and investigations into how a cancer diagnosis affects the care given for other long-term conditions.

In summary, the anatomy of multimorbidity involves a multifaceted coexistence of chronic diseases spanning multiple organ systems, frequently including both physical and mental health conditions, shaped by biological, social, and environmental factors, wanting for multidisciplinary team approach to management and care.

DECLARATION

Consent for publication: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Availability of supporting data:The patient's medical record is available at the hospital for review.

Competing interests: There is no competing interest on behalf of the authors in reporting this case:

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Authors' contributions: All the authors are the multidisciplinary team physicians taking care of the patient and contributed to this case study.

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Authors' information: All authors are doctors affiliated with the Asian Hospital and Medical Center, where the patient received his care.

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