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Case Report

Metastatic GIST with a TWIST of RCC: A case report

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ABSTRACT

Background and Aim: Gastrointestinal Stromal Tumors (GIST) is a tumor of mesenchymal origin in the digestive tract, arising from Interstitial cells of Cajal. Majorly, they are an incidental finding in people of older age group (>60 years) with very rare bone metastasis. Our aim is to understand the role of genetic mutations in metastasis of GIST and coexistence of other malignancy in the same patient.
Case Report: We present an unusual case of a 75-year-old male with jejunal GIST, managed with resection of the tumor and imatinib, who 15 years later presented with subsequent liver, rare femoral head metastases and coexisting Renal Cell Carcinoma in left kidney.
Conclusion: GIST cases can be associated with different syndromes and malignancies. This necessitates additional work up and long term follow up.

1. Introduction

Gastrointestinal stromal tumors (GIST) is the most common primary mesenchymal tumor of the gastrointestinal tract.[1] In 1998, Kindblom and associates discovered that these tumors arise from the interstitial cells of Cajal.[2] Hirota and colleagues discovered that these tumors express a gain of function mutation, CD117 antigen (C-Kit).[1] While most GISTs occur sporadically, certain types are linked to various syndromes such as Carney-Stratakis syndrome and neurofibromatosis type 1. Additionally, there exists a subgroup of familial GIST syndromes, triggered by inherited mutations in KIT or PDGFRA genes.[2] GISTs have shown an association with other primary malignant neoplasms, including simultaneous presence. The main direction of treatment is surgical resection of tumor with adjuvant chemotherapy.[3] Treatment has changed with the discovery of tumor associated mutations. To improve prognosis associated with GISTs, neoadjuvant therapy with a selective tyrosine kinase receptor inhibitor (TKI), Imatinib mesylate is being utilized.[1] Etiology of Renal Cell Carcinoma is either hereditary or genetic mutation.[4]

There are some case reports and small scale case series which pin down Tyrosin kinase mutation as the base of both GIST and papillary Renal Cell Carcinoma occurring in the same patient but a limitation occurs in view of the sample size being small.[5–9]

2. Case Report

A 75-year-old male visited the Orthopedic OPD in October 2022 with a complaint of difficulty in walking for 4 months. X-ray of the left hip joint demonstrated a lytic lesion in the left sub trochanteric region of the femur (Figure 1 A).

Biopsy from the left femur was taken. Grossly the surgical specimens received were multiple soft tissue pieces, friable and brown in color. All together, they measured 3 x 3x 0.5 cm. Microscopically, the bits studied showed spindle shaped cells arranged in fascicles and whorls with elongated and pleomorphic nuclei (Figure 1 B). Few abnormal

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mitosis (16/10 hpf) were seen. The stroma was fibrous and showed congested capillaries. Immunohistochemical stains demonstrated a strong positivity for DOG-1 and cKIT(CK117). The findings confirmed metastatic GIST in femur. The patient had been diagnosed with jejunal GIST in 2007 for which he had undergone partial jejunectomy and was on Imatinib treatment for 3 years. On reviewing the follow up history from another tertiary care institution, it was found that in January 2019, incidental diagnosis of liver metastasis was made. Biopsy and IHC studies, positive for DOG-1 and CD34 and negative for SMA confirmed metastatic GIST in Liver. The patient received Radiofrequency Ablation (RFA) and Lipidol infusion for the liver metastasis.

Another mass was detected in the left kidney as well, which was reported as Renal Cell Carcinoma with features favoring a low grade tubular epithelial neoplasm. On Immunohistochemistry, the epithelial cells were highlighted by PAX8, CK7, AE1/AE3 and EMA while being negative for Ckit, DOG-1, S100, HMB45, D240, CD31, WT1 and TFE3. He was treated with Transarterial Chemo-Embolisation (TACE) and microwave ablation (MWA) for the renal lesion.

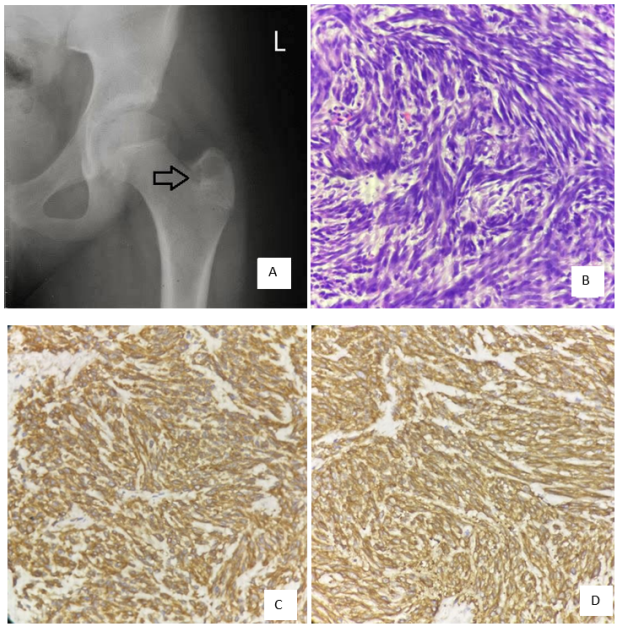

Figure 1: A): X ray of the left pelvis showing lytic lesion in the trochanter of left femur (black arrow); **B)**: GIST: spindle shaped cells with blunt nuclei on and biopsy of bone metastasis (H&E, 40x); **C)**: Immunohistochemistry staining showing expression by tumor cells of CD117/C-KIT (40x); **D)**: Immunohistochemistry staining showing expression by tumor cells ofDOG1 (40x)

3. Discussion

Metastasis of gastrointestinal stromal tumors is a characteristic of a malignant behavior and affects 10% of the GIST patients, with most commonly metastasize in the liver (65%) and peritoneum (21%); GISTs rarely metastasize to lymph nodes (6%), bone (6%), lung (2%)[10,11] and soft tissue (less than 1%).[11] Bone metastases are rare in GIST and favor patients with primary tumors does not include the stomach. An observation was made that patients who had local mass with high risk for recurrence and or malignant tumors with tendency to metastasize were had higher chance to eventually develop bone metastases.[12] Based on the literature, it can be inferred that in instances where metastases from gastrointestinal stromal tumors manifest in uncommon locations, the initial symptoms could aid in pinpointing these sites. Furthermore, employing site-specific imaging techniques for various metastatic sites could refine the characterization of the metastases, while the results of pathological or immunohistochemical analyses could serve to validate the diagnosis.

In our case, the patient incidentally had liver metastasis and later developed bone metastasis as well. Microscopically, they can present as highly cellular mesenchymal tumor of the gastrointestinal tract composed of spindle cells, epithelioid cells or a combination of both. Tumor size, mitotic rate and tumor site are considered as the most important prognostic parameters for patients.[13] Our specimen was from the bone metastasis and had a mitotic rate of 16/ 10 hpf. Though, small size or low mitotic rate could not exclude the malignant potential of the tumor.[14] GISTs are driven by gain-of-function mutations in KIT or PDGFRA (platelet derived growth factor receptor alpha) receptor tyrosine kinase gene. Most GIST lesions stain positive for CD117(C-Kit), CD34, and/or DOG-1.[15] Primarily, they occur in the stomach (50%-70%) or small intestine (20%-30%).

Specific to RCC, which is the most common malignant tumor in the kidney, the majority of cases have mutations of the VHL gene.[16] It usually has an asymptomatic presentation, explaining the late presentation and a poor survival prognosis.[17] The primary sites for metastasis in renal cell carcinoma (RCC) are typically the lungs, with bone involvement occurring in 20–35% of cases, followed by metastasis to lymph nodes, the liver, adrenal glands, and the brain. In patients with metastatic disease, the median survival rate is approximately eight months, with a 50% mortality rate within the first year and a five-year survival rate of only 10%.[18]

The relationship that both conditions has is significant due to both sharing the same pathology of the genetic mutations in the tyrosine kinase pathway.[19] In RCC, the majority of cases are dependent on mutations of the VHL gene. Typically, VHL byproducts bind to transcriptional

factor hypoxia inducible factor (HIF-1α), leaving it inactive. Mutations in VHL cause HIF-1α to become active and bind to cofactors leading to increase in VEGFR which leads to cell growth. Tyrosine kinase is a regulator of these proteins.[19,20] Co-relation of GIST with RCC might prove to be useful for assessing multiple-organ tumors and genetic counseling. Further genetic testing to identify specific mutations is required.

Co-existance of GISTs can either be synchronous or metachronous. GISTs of gastric origin showed the highest rates of coexistence with other malignancies. GISTs were predominantly associated with cancers of gastrointestinal carcinomas, lymphoma/leukemia, and carcinomas of prostate.[21] The E-GISTs are cytologically and histologically similar to GISTs but usually behave more aggressively, with high metastatic potential and a high recurrence rate.[22]

4. Conclusion

Follow up in every patient of treated GIST is essential. Metastasis of GIST though rare can occur after several years. Also, Screening for other malignancies in such cases of GIST is clinically significant as majority of these tumors harbor oncogenic mutations of the KIT receptor Tyrosine Kinase which can aid in early diagnosis as well as in targeted therapy. Important because of its association with other cancers. Molecular studies and targeted therapies in such cases can help in diagnosis, prevention and management of multiple-organ tumors.

5. Sources of Funding

None.

6. Conflict of Interest

None.

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