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Bone marrow metastasis of testicular germ cell tumour: A rare case

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ABSTRACT

Germ cell tumour (GCT) is the most common testicular tumour that commonly presents as a painless mass. Bone marrow metastasis in cases of testicular GCT is rare; only few case reports are available till date in the literature. Here an adult male presented with an intra-abdominal mass in right iliac fossa with inguinal lymphadenopathy with a deranged kidney function test. Bone marrow (BM) aspirate smear revealed metastatic tumour cells, but BM-biopsy was unremarkable. High serum Beta - HCG (38286 mIU/L) pointed towards germ cell lesion. Lymph node biopsy along with immunomarkers confirmed metastatic foci from germ cell tumor and managed as per standard protocol. Rarely BM aspirate is seen positive for malignancy, while biopsy turns out to be negative. Secondly, BM metastasis of GCT should be considered while dealing with cases like this.

Informed consent: This is certified that the informed consent has been obtained from the patient.

1. Introduction

Germ cell tumour (GCT) is the most common testicular tumour. It is the most common solid malignancy in young male adults [1,2]. Asian countries account for 27.2% of testicular tumours and 56.5% of cancer-related deaths due to testicular tumours (WHO cancer statistics 2018). GCT can be classified into 2 major histological types: seminoma and non-seminoma germ cell tumours (NSGCT). Seminoma comprises about 40%–50% of GCTs, while NSGCTs comprise 50%–60% of all GCTs [3].

In the initial stage, testicular tumours commonly present as a painless testicular mass. The International Germ Cell Consensus (IGCC) classifies metastatic NSGCT into good, intermediate, and poor risk groups using various parameters like the primary site, presence of non-pulmonary visceral metastases, and tumour markers alpha-fetoprotein (AFP), human chorionic gonadotrophin (HCG) and lactate dehydrogenase (LDH). Non-pulmonary visceral metastasis and tumour markers are among the important prognostic factors. Around 20% of seminomas present with metastasis at the time of diagnosis because of their less aggressive nature, whereas approximately 30% of nonseminomatous germ-cell tumours (NSGCT) of the testis present with metastatic disease [4]. Most commonly reported sites of metastasis from a testicular germ cell tumour are retroperitoneal lymph nodes, mediastinal lymph nodes, lungs, liver,

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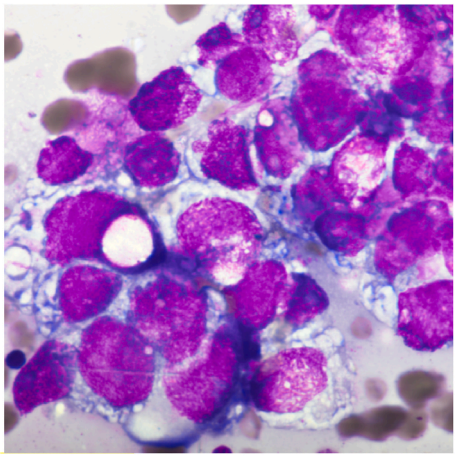
Abbreviation

GCT	Germ cell tumour
BM	Bone Marrow Metastasis
AFP	alpha-fetoprotein
HCG	human chorionic gonadotrophin
LDH	Lactate dehydrogenase
NSGCT	nonseminomatous germ-cell tumors
CBC	complete blood count
IGCCC	International Germ Cell Consensus Classification

gastrointestinal tract, spleen, liver, and adrenal glands [5].

The objective of this manuscript is to highlight the importance of bone marrow aspirate over bone marrow biopsy in finding metastatic foci. Metastasis to bone marrow is very rare in cases of testicular germ cell tumours and only a few isolated case reports have been published till date [6]. We present a case of primary testicular germ cell tumour metastatic to bone marrow in a 45-year-old male.



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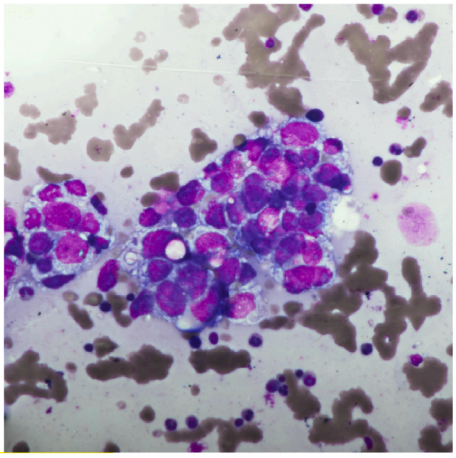

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Fig. 1. A: Bone marrow aspirate smear, May Grunwald-Giemsa stain, 1000X, B: Bone marrow aspirate smear, May Grunwald-Giemsa stain, 400X.

2. Case report

An individual male in his forties presented with complaints of abdominal distension, constipation, unexplained fever and weight loss for the past three months. He had no signs of comorbidities but had a history of surgery for right inguinal region swelling (possibly right undescended testis) three months back. No records of any surgical details were available for the same. On clinical examination, he had 6 × 5 cm intra-abdominal mass in the right iliac fossa, multiple large bulky B/L inguinal lymph nodes, and hepato-splenomegaly. On scrotal examination, right testicle was missing. His complete blood count (CBC) and hemogram were within normal limits. At the same time, the biochemical parameters showed deranged urea, serum creatinine, uric acid, and 24-h urine protein levels with values of 112 mg/dL, 5.2 mg/dL, 12.4 mg %, and 74 mg/dL, respectively. Liver function test values were also within normal limits, but serum albumin was slightly decreased (3.10 g/dl). Ultrasonography of lower abdomen revealed multiple enlarged lymph nodes in the left iliac fossa and the right inguinal region. Lymph node of the left iliac fossa was large in size and measured 10.9 × 5.4 cm. It was found to compress the left ureter causing hydronephrosis of left kidney. CT and MRI of the abdomen also confirmed the same and also revealed multiple hypointense lesions in the liver. Based on the clinical symptoms and radiological findings a diagnosis of intra-abdominal lymphoma metastatic to liver was made.

To work-up for lymphoma, bone marrow aspirate (BMA) with biopsy was performed. BMA examination showed focal clusters of metastatic tumour cells were noticed, which were very distinct from normal hematopoietic cells (Fig. 1A and 1B). These tumour cells were in cohesive clusters and large in size. They had a high N/C ratio, a large pleomorphic nucleus with 0–1 prominent nucleoli, and a moderate amount of vacuolated cytoplasm. However, the imprint cytology and biopsy were negative for any evidence of metastasis. A metastatic carcinoma to bone marrow diagnosis was suggested, and further work-up was advised to look for the primary site of carcinoma.

Patient was thoroughly evaluated after the findings of bone marrow aspirate examinations and further biochemical investigations revealed elevated levels of Beta - HCG (38286 mIU/L, reference range 200–800 mIU/L), LDH (5345 U/L, reference range 140–280 U/L) and AFP (21.88 ng/ml, reference range 0–40 ng/mL). Biopsy of inguinal lymph node revealed sheets of large polygonal tumor cells with abundant vacuolated cytoplasm and large pleomorphic nucleus (Fig. 2A and B). Immunohistochemistry (IHC) showed positivity for SALL-4 (Fig. 2C), CD117 (Fig. 2D) and negative for LCA (CD 45) (Fig. 2E), and CD 30 (Fig. 2F). Based on these new findings it was postulated that the previous surgery of right inguinal swelling might be a case of cryptorchidism. A final diagnosis of nonseminomatous germ cell tumor metastatic to the lymph nodes, liver and bone marrow was made (stage T4 N3 M1b).

The patient was started on a PEB regimen comprising bleomycin, etoposide, and cisplatin as per standard protocol. The prescribed doses for drugs are Bleomycin: 30 units/m^2, days 1, 8 & 15 (maximum 30 units); Etoposide: 100 mg/m^2, days 1–5 and Cisplatin: 20 mg/m^2, days 1–5. No any notable complication was seen with the patient following these drugs. Following chemotherapy, palliative

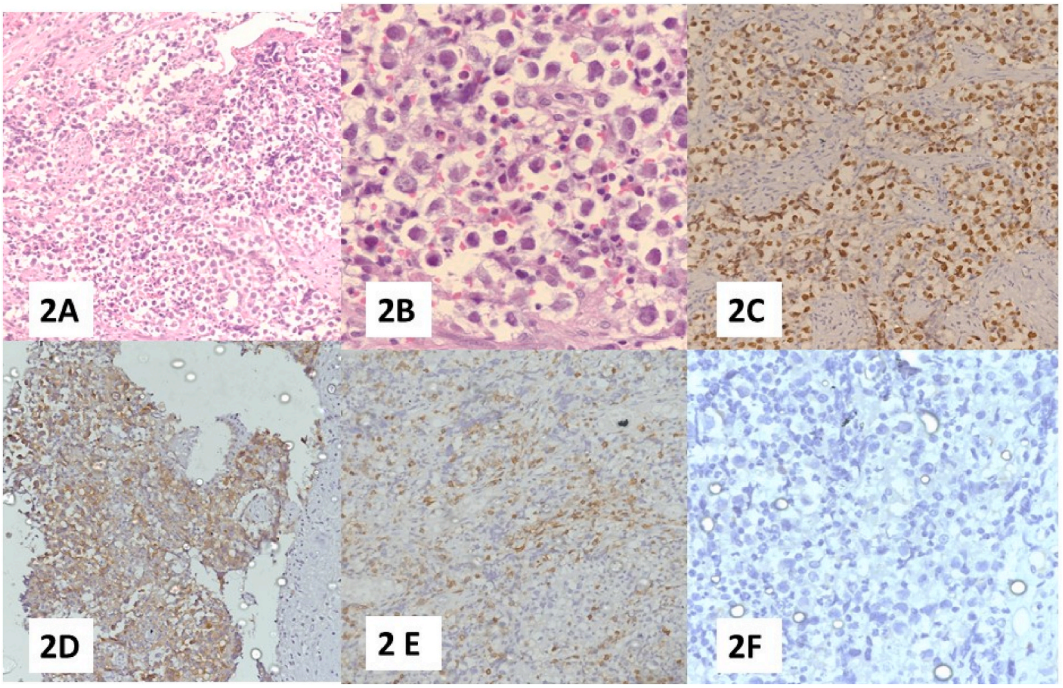

Fig. 2. A: Histopathology of inguinal lymph node showing tumour cells, H & E 100X; B: Histopathology of inguinal lymph node showing tumour cells, H & E 400X; 2C: Immunohostochemistry of showing tumour cells, positive for SALL4, 100X; 2D: Immunohostochemistry of showing tumour cells, positive for CD117, 100X; 2E: Immunohostochemistry of showing tumour cells, negative for LCA (CD45), 100X; 2F: Immunohostochemistry of showing tumour cells, negative for CD30, 100X.

radiotherapy was given to spine and hemipelvis 20 Gy/10 Fractions + boost 10 Gy/5 Fractions. Again, no any notable complication was seen with the patient following chemotherapy or radiotherapy. The patient is still on follow-up and in good condition.

3. Discussion

Asian countries account for 27.2% of the testicular tumours and 56.5% of cancer-related deaths. Incidence rates for new cases of testicular cancers are rising, with an average increase of 0.8% each year over the last 10 years. Approximately 0.4% of men are being diagnosed with testicular cancer at some point during their lifetime, based on 2013–2015 data [7]. Tumours of the testis account for only 1% of all solid malignancies in men. However, it is becoming one of the most commonly diagnosed malignancies in the reproductive age group [8,9]. At diagnosis, approximately 50% and 5% of nonseminoma (NSGCT) and seminoma patients have evidence of bulky retroperitoneal disease or distant metastases [10,11]. This is due to the aggressive nature of the NSGCT compared to seminomatous GCTs. In 1997, the International Germ Cell Consensus Classification (IGCCC) was published, which became the gold standard for treating and prognosticating both seminomas and Non-seminomatous germ cell tumor (NSGCT) [3]. NSGCT was stratified into good, intermediate, and poor risk groups based on the location of the primary tumor, presence or absence of non-pulmonary visceral metastasis, and levels of tumour markers (Beta HCG, AFP, and LDH levels). Among these, the five-year progression-free survival was 90%, 69%, and 55% for patients with good, intermediate, and poor prognoses, respectively [3]. The small subset of patients with very high levels of the serum tumor markers, presence of non-pulmonary visceral metastases, and mediastinal extragonadal NSGCT have an inferior prognosis which influences the choice of chemotherapy regimen and number of cycles [10]. However, with the advent of cisplatin-based chemotherapy since 1978, cure rates have improved dramatically, making testicular tumour as one of the highly curable cancers.

Metastasis from testicular tumours is commonly reported from retroperitoneal lymph nodes, mediastinal lymph nodes, lungs, liver, gastrointestinal tract, spleen, liver, and adrenal glands [5]. Testicular malignancy spreads via lymphatics to retroperitoneal lymph nodes, then via a thoracic duct to paraaortic lymph nodes, followed by mediastinal and supraclavicular lymph nodes [6]. Hematogenous spread also occurs in the lungs, brain, bone, and liver [6]. But bone marrow as a site of metastasis for GCTs is very rare. Hitchins et al. studied 297 patients with metastatic testicular and extragonadal germ cell tumour, and only 3% of these had bone metastasis at first presentation and 9% at the time of relapse. However, none of the patients had bone marrow metastasis [12]. Oechsle et al. studied 434 patients with poor-risk GCT stratification and found only 9% of patients presented with bone metastasis, and none of them had bone marrow involvement [13]. Kilickap et al. studied 73 cases of bone marrow metastasis. Breast and lung cancer were the most common tumor metastasizing to bone marrow, followed by gastric cancer, prostate cancer, and Ewing sarcoma [14]. NSGCT has been reported to cause bone marrow metastasis in 3 cases till date, as per the literature available [15]. To the best of our knowledge, this is the second case of testicular germ cell tumour metastasizing to bone marrow besides a single case of mixed germ cell tumor metastatic to marrow reported by Kumar et al. [6].

Wang J et al., 2015 studied the role of radiotherapy (RT) in a series of cases of NSGCT. They compared the management of NSGCT between two groups, one who received RT along with chemotherapy and or surgery and the other group was that who received chemotherapy and or surgery without RT. A significant difference was found between the two groups. Cases who received RT had higher five years overall survival ($P = 0.043$) and progression free survival ($P = 0.023$) [16]. So, palliative radiotherapy is now recommended in NSGCT. In case of metastasis, the affected area is irradiated. The dose of RT depends up on site and the size of involvement [17].

3.1. Limitations of the study

Following the first surgery, a histopathological examination of the tissue was not done. It led to the start of initial therapy for GCT delayed. The limitation of a case report is that the findings can be used for a cohort. Rare events would be kept in mind while dealing with the patients' health care.

3.2. Findings supported by data

Ruchita T et al. (2018) showed that in 14.3% of cases, metastasis couldn't be detected in bone marrow (BM) aspirate, while all these cases were positive for the same in BM biopsy. They showed all of their cases had metastatic foci in BM biopsy [18]. Sharma et al. showed that metastasis can be found in BM aspirate smears, while biopsy may be negative [19]. Chauhan et al. supported the findings of Sharma et al. They saw it in lung cancer. They postulated that this condition may happen when the piece of bone marrow is of inappropriate length [20].

4. Conclusion

Rarely BM aspirate is seen positive for malignancy, while biopsy turns out to be negative. Secondly, BM metastasis of GCT should be considered while dealing with cases like this. Metastasis of germ cell tumour in bone is seen in 3% of cases, but its metastasis in bone marrow is extremely rare. Only a few case reports are available. Bone marrow biopsy is considered a better diagnostic importance over BM aspirate, while in this study, BMA smear proved to be better in detecting metastatic foci. In India, HPE has not become the routine practice after surgical excision in many parts of the country, possibly due to the unavailability of a histopathologist. This results in misdiagnosis of many cases at an early stage.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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