



CASE REPORT

# Neoplastic Fever: A Rare Differential of Intractable Fever

Swati Agrawal<sup>1</sup> · Ratna Biswas<sup>1</sup> · Himani Kundoo<sup>1</sup> · Shivangi Shanker Srivastava<sup>1</sup> · Divya Kanwar<sup>1</sup> · Anujna Tumpati<sup>1</sup>

Received: 6 July 2022 / Accepted: 26 February 2023 / Published online: 17 March 2023  
© Federation of Obstetric & Gynecological Societies of India 2023

## Introduction

Neoplastic fever, a paraneoplastic syndrome, is a rare entity attributed to cytokine-mediated effect of the malignancy. The common causes of fever associated with malignancy, such as infection, neutropenia, transfusion, thrombosis, and drug reaction, make it a diagnostic challenge. Specifically, there is paucity of literature with respect to neoplastic fever in ovarian malignancies.

Yolk sac tumor of ovaries is a highly aggressive malignant germ cell tumor with a poor prognosis. Timely diagnosis and prompt treatment are the key to management in this condition. However, unusual presentations can delay definitive management as happened in our case. We present a rare case of a yolk sac tumor with high-grade fever as the chief complaint which was later diagnosed as neoplastic fever during the course of management.

## Case Report

An 18-year-old unmarried girl presented to our emergency with a history of high-grade fever for two weeks associated with abdominal lump which was insidious in onset and rapidly increased in size over a period of one week. The fever was sudden in onset, not associated with chills and rigors without other localizing signs or symptoms. It was temporarily relieved with paracetamol only to recur again and was not responsive to over the counter antibiotics.

At the time of presentation, the patient had an Eastern Cooperative Oncology Group (ECOG) performance score of 3, high-grade fever (104 °F), tachycardia (106 bpm), and severe anemia. She had decreased breath sounds in right basal zone on chest examination with no added sounds, and abdominal examination revealed a large abdominopelvic lump corresponding to 32 weeks size gravid uterus which was occupying all the quadrants, firm, immobile, non-tender with irregular margins, and overlying normal skin.

The patient was evaluated for fever and empirically started on injectable broad-spectrum antibiotics in view of raised leucocyte count (20,000/mm<sup>3</sup>, DLC-N86, L8, M5, E1B0). She had a hemoglobin of 5.8 gm% (MCV-111.4, MCH-34.7 AND MCHC-31.2) with normal liver and kidney function tests. All her body fluid samples were sent for culture and sensitivity before the institution of antibiotics, which came back negative. CECT chest showed a right pleural effusion of 3.2 mm with collapse of underlying lung, athletic bands, and few enlarged supraclavicular lymph nodes (up to 12 mm). Pleural fluid cytology was negative for malignant cells and tuberculosis.

The CECT abdomen was suggestive of large abdominopelvic mass (19 × 11 × 18cm) arising from right adnexa with vascular solid component and enhancing internal septations (Fig. 1). Tumor markers showed raised alpha fetoprotein (AFP) levels (> 3000 ng/ml) and LDH (899 IU/l). These findings were highly suggestive of a malignant ovarian yolk sac tumor.

---

Dr. Swati Agrawal is Professor in the Department of Obstetrics & Gynaecology at Lady Hardinge Medical College, New Delhi, India; Dr Ratna Biswas is Director Professor, Department of Obstetrics & Gynaecology at Lady Hardinge Medical College, New Delhi, India; Dr Himani Kundoo is a Senior Resident, Department of Obstetrics & Gynaecology at Lady Hardinge Medical College, New Delhi, India; Dr Shivangi Shanker Srivastava Srivastava is a Junior Resident, Department of Obstetrics & Gynaecology at Lady Hardinge Medical College, New Delhi, India; Dr Divya Kanwar is a Junior Resident, Department of Obstetrics & Gynaecology at Lady Hardinge Medical College, New Delhi, India; Dr Anujna Tumpati is a Junior Resident, Department of Obstetrics & Gynaecology at Lady Hardinge Medical College, New Delhi, India.

---

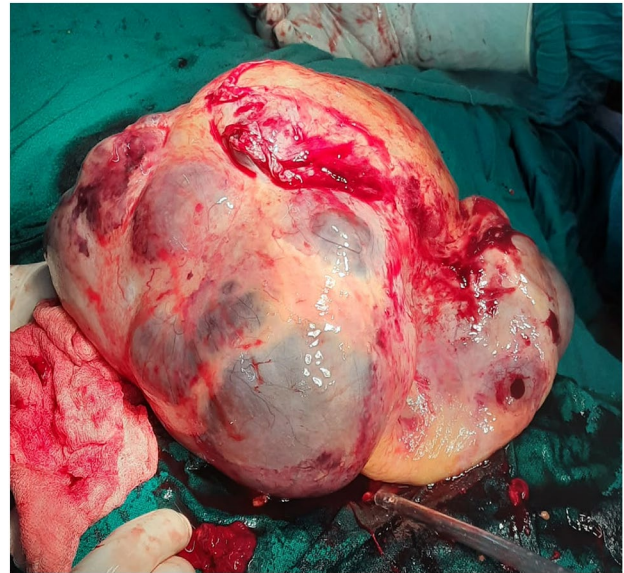
✉ Himani Kundoo  
hm8390@gmail.com

<sup>1</sup> Department of Obstetrics and Gynaecology, Lady Hardinge Medical College, New Delhi, India



**Fig. 1** CT picture showing a large abdomino-pelvic mass (19×11×18 cm) having predominantly cystic component with few solid enhancing areas within

After discussion with the tumor board, the patient was planned for primary cytoreductive surgery but declared unfit in view of persistent high-grade fever and severe anemia. Antibiotics were stepped up. Since the fever was not responding to antibiotics and the TLC was persistently high, empirical antitubercular treatment (ATT) was started on the basis of chest findings, despite a negative tuberculosis screen. The diagnosis of neoplastic fever was considered after the patient failed to respond even to empirical ATT. Subsequently, naproxen test was administered (375 mg of naproxen twice a day for 2 days). Her pleural fluid culture report showed a growth of acinetobacter sensitive to levofloxacin, and patient was started on levofloxacin on the same day as naproxen. The fever of the patient abated, and she was given blood transfusions to build her up for surgery. After 48 h of stopping naproxen, the patient developed fever again. And there was no change in her TLC while still being on levofloxacin which confirmed that the fever had responded to naproxen and not levofloxacin. Naproxen was given again to the patient to settle fever, and she was taken up for staging laparotomy. Right salpingoophorectomy with removal of solid cystic mass with bilateral pelvic lymphadenectomy with infracolic omentectomy was done (Fig. 2). The histopathology report confirmed a malignant yolk sac tumor, stage pT1aN0Mx limited to the ovary with negative lymph nodes, and omentum. In the post-operative period, the patient was



**Fig. 2** Intraop picture showing solid cystic mass measuring 20×19 × 15 cm

afebrile, her AFP levels declined, and leucocyte counts drastically decreased (HB-8.7, TLC-11,690, DLC-N73.9, L13.9). The continued afebrile state of the patient post-surgery further corroborated our diagnosis of neoplastic fever. Her ATT was stopped, and she was planned for 4 cycles of bleomycin, etoposide, and cisplatin (BEP) chemotherapy in consultation with the medical oncology department and discharged in satisfactory condition.

On follow-up, patient tolerated first cycle of chemotherapy well and her AFP after first cycle was 109 ng/ml.

## Discussion

Fever in malignancy patients can be attributed to a wide spectrum of causes, but it is important for clinicians to consider the diagnosis of neoplastic fever as a part of the paraneoplastic syndrome, if other causes are ruled out.

The exact etiology is elusive, but it has been attributed to release of pyrogenic cytokines (interleukin-1, interleukin-6, and tumor necrosis factor) from tumor cells or macrophages responding to these tumor cells. These cytokines induce prostaglandin E2 synthesis which acts on the preoptic nuclei of hypothalamus to reset the thermostatic set point.

Unfortunately, there is no fever pattern specific to neoplastic fever. Some authors have reported features like low incidence of chills and rigors, no or minimal tachycardia, mental changes, less response to acetaminophen, and more dramatic defervescence with NSAIDs such as naproxen. In our case, the tachycardia was continuous, irrespective of fever, and can be attributed to severe anemia. In another

case reported by Kansara et al. [1], the patient reported with high-grade fever and overt hypothyroidism. As in our case, fever was persistent, with no other identifiable cause and resistant to empirical antibiotic therapy. In their case also, fever disappeared after cytoreductive surgery.

Zell and Chang have proposed the following diagnostic criteria for neoplastic fever [2]:

- I. Temperature over 37.8 °C at least once each day
- II. Duration of fever over 2 weeks
- III. Lack of evidence of infection on
  - a. Physical examination
  - b. Laboratory examinations, e.g., sputum smears or cultures, cultures of blood, urine, stool, bone marrow, spinal fluid, pleural fluid, and discharge from local lesions
  - c. Imaging studies, e.g., chest radiograph and computed tomographic scans of the head, abdomen, and pelvis
- IV. Absence of allergic mechanisms, e.g., drug allergy, transfusion reaction, and radiation or chemotherapeutic drug reaction
- V. Lack of response of fever to an empiric, adequate antibiotic therapy for at least 7 days
- VI. Prompt, complete lysis of fever by the naproxen test with sustained normal temperature while receiving naproxen

Neoplastic fever is commonly associated with certain malignancies like hematological, colon, renal cell carcinoma, cholangiocarcinoma, etc. [3], but its association with ovarian malignancy is very rare. Yolk sac tumor or endodermal sinus tumor is the second most common malignant ovarian germ cell tumor (MOGCT). It is rare and accounts for about 1% of ovarian malignancies and 14.5–16.4% of all the MOGCTs, usually presenting in the second or third decade of life with a brief duration of symptoms. The most common symptom is pain abdomen, followed by abdominal mass, pressure symptoms, menstrual disturbances, ascites or peritonitis secondary to torsion, infection, or rupture of ovarian tumor. Unusual presentations of yolk sac tumors

include endocrine abnormalities, fever, and non-malignant pleural effusion [1]. Neoplastic fever is a rare presentation of MOGCTs with very few cases reported in literature [4]. Lack of any obvious cause for fever, response to naproxen, as well as complete resolution of fever within 24 h of surgical treatment favored the definite diagnosis of neoplastic fever in our case.

## Conclusion

The authors conclude that possibility of neoplastic fever should be considered in all cases of suspected ovarian malignancy with fever. There is paucity of data on the incidence of neoplastic fever in ovarian malignancies. Nevertheless, keeping this condition in the differential diagnosis can help in early diagnosis and aid in avoiding delays in management of such patients.

## Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

**Informed Consent** An informed consent was taken from the patient for the publication.

## References

1. Kansara M, Yadav G, Gothwal M, et al. Yolk sac tumour of ovary with fever and overt hypothyroidism: rare clinical presentation. *BMJ Case Rep.* 2020;13(1):e232114.
2. Zell J, Chang J. Neoplastic fever: a neglected paraneoplastic syndrome. *Support Care Cancer.* 2005;13(11):870–7.
3. Pasikhova Y, Ludlow S, Baluch A. Fever in patients with cancer. *Cancer Control.* 2017;24(2):193–7.
4. Ray-Coquard I, Morice P, Lorusso D, et al. Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2018;29:iv1-8.

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.