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CLINICOPATHOLOGICAL PROFILE OF PATIENTS WITH SYNCHRONOUS MALIGNANCY AND TUBERCULOSIS- A CASE SERIES WITH A REVIEW OF THE LITERATURE

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ABSTRACT

Cancer and tuberculosis are two of the most common causes of morbidity and mortality and a major health problem but their coexistence is rarely encountered. Cancer patients are more susceptible to infections due to immunosuppression by either disease or treatment-related toxicity. This case series aims to present a clinicopathological profile of patients with coexistent carcinoma and tuberculosis because pathological and practical implications of their existence are less pursued.

KEYWORDS

Malignancy, Tuberculosis (TB), Coexistence, Caseation, Epithelioid granuloma, Ziehl-Neelsen (ZN) stain, antitubercular therapy (ATT).

INTRODUCTION:

Bayle described Cavitation Canceruse which described the association of TB with cancer nearly 200 years ago.[1] Susceptibility of cancer patient to infections is due to their immunocompromised state. The World Health Organization (WHO) TB statistics for India for 2021 give an estimated incidence figure of 2,590,000 cases. This is at a rate of 188 per 100,000 population.[2] Lung, skin, and larynx cancer have been described along with tuberculosis. [1] The disease affects the intestinal tract, lymph nodes, peritoneum, and solid organs in varying combinations.[1] India is an endemic location for TB hence a greater burden of TB's association with malignancy is seen. The resurgence of TB in the developed world is on the rise due to the increased use of chemotherapy and steroids.

Even though being an endemic country, the clinicopathological and practical implications of their coexistence have received little attention. As research for carcinogenesis is expanding possible correlation between chronic inflammation and cancer development is slowly being unraveled. Cancer or chemotherapy leads to depressed T cell function hence leading to either reactivation of a latent TB infection or rarely acquisition of a primary mycobacterial infection.[3]

History of TB infection has been examined as a risk factor for cancer development but whether it facilitates cancer is yet to be determined.

Case series

Case 1

A 61-year-old female patient presented with pain in the abdomen for 1 month. The patient **was** a known case of **diabetes** mellitus, hypertension, and hypothyroidism. Her hemoglobin **was** 10.4 gm%, total leukocyte count of 6,000/mm3, and an Erythrocyte sedimentation rate (ESR) of 15 mm/**h** with normal liver function test, kidney function test, and blood sugar **levels. The patient was Non- Reactive for** Human immunodeficiency virus (HIV) and **with** no history of tuberculosis **or jaundice**. Ultrasonography of the Abdomen and pelvis reported gall bladder mass. Echo and chest X-ray showed normal findings. Contrast-enhanced Computed Tomography (CECT) abdomen and pelvis reported a hypodense heterogeneously enhancing mass measuring 38 x 37 mm arising from the body and fundus of the gall bladder extending up to liver parenchyma. **The** common bile duct **was** mildly prominent and a lesion measuring 9.5 x 7.0 mm in the right lobe of the liver **showed** peripheral nodular enhancement **(Figure 1: 1a).** Radical cholecystectomy with segmentectomy was performed. Histopathological examination revealed Adenocarcinoma, biliary type **(Figure 1: 1b)**. **TNM Staging pT3N1 (Stage IIIB).** Hepatoportal lymph node **was** positive for metastasis **with extra nodal extension (ENE) and also caseating necrosis with epithelioid granulomas seen**. **(Figure 1: 1c).** Ziehl–Neelsen (ZN) stain for acid-fast bacilli was negative. The WHO Category I antitubercular therapy (ATT) with isoniazid, rifampicin, pyrazinamide and ethambutol was started on postoperative day 15, and she received adjuvant radiotherapy **as it was positive for ENE**. She is doing well on follow-up.

Case 2

A 48-year-old female presented with complaints of pain in the abdomen for 6 months. She **had** no comorbidities. Her hemoglobin **was** 10.6 gm%, total leukocyte count of 11,200/mm3, and an ESR of 20 mm/**h** with normal liver function test, kidney function test, and blood sugar **levels. The patient was Non- Reactive for** Human immunodeficiency virus (HIV) and **with** no history of tuberculosis. Echo and chest X-ray showed normal findings.CA-125 level was raised to 143.4 units/mL. CECT (Contrast-enhanced Computed Tomography) abdomen and pelvis **was** reported **as** a well-defined heterogeneously enhancing solid cystic mass measuring 91x89x88 mm in the right adnexa and 67x69x65 mm involving left adnexa, likely bilateral malignant cystadenoma. Multiple enlarged pre, para-aortic, and bilateral common iliac lymph nodes **were** seen as likely **metastatic (Figure 2: 2a).** Tru cut biopsy from the adnexal mass showed **a** malignant surface epithelial tumor ovary. **Then she had received three cycles of paclitaxel and carboplatin as adjuvant chemotherapy**. After 3 months, CECT again revealed heterogeneously enhancing mass. **So,** she then underwent **interval** cytoreduction **of which** histopathological examination **was** reported **as** malignant surface epithelial tumor of bilateral ovaries**, Grade-II, CRS-2 (Figure 2: 2b)**. **TNM Staging ypT1bN1b (Stage IIIA1).** Granulomatous inflammation of the endometrium and left fallopian tube along the pelvic lymph node **was** present **(Figure 2: 2c)**. Left and right pelvic lymph nodes showed caseation with epitheloid granulomas and was positive for metastasis **also**. Ziehl–Neelsen (ZN) stain for acid-fast bacilli was negative. The WHO Category I antitubercular therapy was started on postoperative day 10 **for 6 months along with three more cycles of paclitaxel and carboplatin as adjuvant chemotherapy. The patient is doing well on follow-ups.**

Case 3

A 47-year-old female patient presented in OPD with a swelling in the left breast associated with pain for 2 weeks**. Her grandmother had a history of breast cancer**. Clinical examination showed a firm lump in **the** left breast. Blood investigations and Chest X-rays were normal. **The patient was Non- Reactive for** Human immunodeficiency virus (HIV) and **with** no history of tuberculosis. Mantoux's test was positive. A mammogram of the left breast showed an irregular hypoechoic mass measuring 3.4x2.2 cm in the upper outer quadrant **(Figure 3: 3a and 3b).** USG-Guided FNAC (Fine Needle Aspiration Cytology) showed atypical cells, suspicious for malignancy. Trucut biopsy showed Invasive Duct Carcinoma- No specific type **Grade-3** with apocrine differentiation. Immunohistochemistry was negative for Estrogen and Progesterone and 3+ positive for Her2neu. Ki67 was 28-30%. PET-Scan reported a hypermetabolic enhancing soft tissue lesion in the upper outer quadrant of the left breast measuring 3.2x2.3x2.3 cm **(Figure 3: 3c)**. Hypermetabolic left axillary, retro pectoral, and cervical lymph nodes show metastatic nature. USG-Guided biopsy of the right cervical level II lymph node revealed tubercular lymphadenitis **(Figure 3: 3d).** Later left side breast conservation surgery was done with lymph node dissection **of which** histopathological examination revealed Invasive Duct Carcinoma with medullary features, Grade 3. **TNM Staging ypT1cN0(Stage IA).**

The WHO Category I antitubercular therapy was started soon after a week. She then received paclitaxel along with trastuzumab as adjuvant chemotherapy. After few months she had received 52.5 Gy/20 cycles in a phasic manner using the IGRT technique. She is doing well on successive follow-ups.

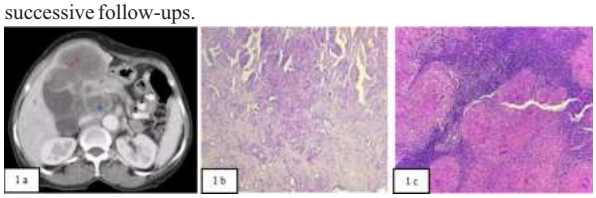

Figure 1: (1a)- NCCT axial image shows heterogeneously enhancing mass arising from the fundus of gall bladder infiltrating into segment 4b of the liver (red arrow) with multiple enlarged necrotic portal lymph nodes (blue arrow). **(1b)-** histopathological image from gall bladder shows Adenocarcinoma, moderately differentiated Biliary type. **(1c)-** Hepatoportal node shows caseating epithelioid granulomas with giant cells.

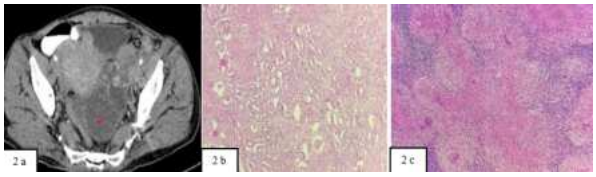

Figure 2: (2a)- CECT abdomen and pelvic, axial image show peripherally enhancing cystic lesion arising from the left ovary (red arrow) with necrotic lymph nodes in the pelvis (black arrow). **(2b)-** Histopathological image from ovarian mass shows residual malignant surface epithelial tumor- Grade 2. **(2c)-** Left pelvic node shows caseating epithelioid granulomas with giant cells.

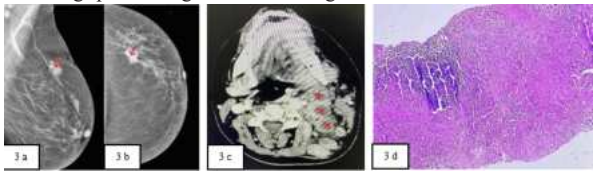

Figure 3: (3a and 3b)- Mammogram ML view and CC view of left breast show radiopaque lesion with speculated margins in the upper inner quadrant. **(3c)-CECT** neck Coronal image showing enlarged necrotic conglomerate right submandibular lymph node (red arrow). **(3d)** -The Trucut biopsy from the right cervical lymph node shows caseating epithelioid granulomas with giant cells.

DISCUSSION:

Chronic inflammatory conditions increase cell turnover, leading to genetic errors.[4] Mycobacterial Tuberculosis can induce DNA damage.[5] Both DNA damage and chronic inflammation together can lead to mutagenesis.[6] Chronic inflammation leads to enhanced angiogenesis, all leading to a carcinogenic microenvironment.[6] Also, inflammation and fibrosis caused by TB, can induce genetic damage which increases the risk of malignancy.[7]

The synchronous association of malignancy and TB occurs as a coincidence without any relationship; secondary infection because of immunosuppression or cancer developing in an old TB focus.[8]

Various studies have reported simultaneous or sequential occurrences of TB and lung cancer. The association between these two diseases is important since both are quite prevalent and have a major impact on public health.[7] Silva et al. described 24 cases of lung cancer with tuberculosis. Of which lung cancer and tuberculosis occurred simultaneously in 10 cases and 14 cases had previous history of TB.[7] In our case series as summarized in Table 1 and Table 2, all were extrapulmonary tuberculosis and were diagnosed along with cancer. None of the patients had any other reason for an immunocompromised state except that of cancer. None of the patients had a previous history of tuberculosis or any recent contact with a person having tuberculosis. Hence, their coexistence can be explained by the mechanisms mentioned and by reactive oxygen species or nitrogen species produced by activated neutrophils which bind to the DNA, induce genetic change and neoplastic transformation.[9]

Clinically it is difficult to diagnose their coexistence because of similar and nonspecific features of TB both clinically and radiologically.[10] Histopathologically, it can be diagnosed by caseating granuloma with Langhans type of giant cells. In our case series, TB was diagnosed by the presence of caseating granuloma. None of them showed AFB positivity.

The first case in our series describes the coexistence of adenocarcinoma gall bladder (GBC) and hepatoportal lymph node tuberculosis. TB can be present as abdominal or peritoneal lymphadenopathy and diffuse peritoneal disease.[11] In the study of 340 patients, by Javed et al, 7 patients have concomitant TB. Out of 7 cases, 2 were detected as supraclavicular TB preoperatively by FNAC, 3 were detected as abdominal TB intraoperatively and 2 were detected postoperatively with histopathological examination showing GBC with tubercular lymphadenitis of the hepatoduodenal lymph nodes.[12] Also the fact that thick-walled GB can have multiple benign pathologies in the endemic zone and malignancy must be considered until proven otherwise as explained by Gupta A. et al[13] There is significant overlap in the clinical and radiological characteristics of GBC and TB GB as seen in the study by Krishnamurthy et al.[14] To conclude an enlarged supraclavicular, para-aortic, or extensive hepatoduodenal lymphadenopathy is mostly due to tuberculosis, and peritoneal tubercles of miliary tuberculosis are mostly a metastatic peritoneal disease from a GBC.[12]

The second case in our series describes concurrent malignant surface epithelial tumors of ovaries along with TB in the endometrium, fallopian tube, and pelvic nodes. The transmission of genital TB occurs through lymphatics, hematogenous, and sexual routes.[15] Pelvic TB is always due to the reactivation of primary TB elsewhere in the body.[16] Genital TB involves 90- 100% fallopian tubes, 50-80% endometrium, 20-30% ovaries, 5-15% cervix, and 1% vulva and vagina.[16] Limited cases have been described in the literature is summarized in Table 3.

The third case in our series describes concurrent Invasive ductal carcinoma of breast and cervical lymph node tuberculosis. Carcinoma breast is one of the most common clinical conditions, but its coexistence with TB is very rare.[18] This is because of the resistance of breast tissue to the survival and multiplication of mycobacterium tuberculosis and ATT.[19] Mammary tuberculosis is usually secondary to old TB focus either pulmonary or in lymph nodes within the paratracheal, internal mammary, or axillary nodal regions.[20] The involvement of breast secondary to TB is usually by direct hematogenous spread.[20] Das et al reported a case of colloid carcinoma of the breast [21] while Pandey et al reported infiltrating ductal carcinoma metastatic to axillary lymph nodes containing tuberculous foci.[1] Ramamoorthy et al described 11 cases of TB with malignancy of which 2 cases had breast cancer along with supraclavicular tubercular lymphadenitis concordant with our case.[10] However, coexistence in the cervical group of lymph nodes is rare. So, the lymph node enlargement in breast cancer is not always caused by metastasis from breast cancer even in ipsilateral lymph nodes.[18] Various cases have been described in the literature is summarized in Table 4.

TB lymphadenitis is one of the most common forms of extrapulmonary tuberculosis. After establishing a pulmonary infection focus, macrophages phagocytose bacilli and can disseminate via the lymphatic system. If immunity is intact bacterial growth is contained. Reactivation occurs whenever an underlying condition affects the immune response, such as malignancy.

Different case reports and case series have been published suggesting possible mechanisms by which TB and malignancy can coexist, but they still lack concrete proof due to the lack of studies. But all these cases had more than one reason for the immunocompromised state. Our case series is different as their immunocompromised state was due to cancer or its treatment.

CONCLUSION:

Simultaneous or sequential occurrence of malignancy and TB occurs due to reactivation of infection in immunocompromised patients is due to cancer not because of cause-effect relationship in between them.[10]

So, the harm in misdiagnosed or undiagnosed cancer with coexistent underlying TB after giving chemotherapy can lead to fatal dissemination of the coexistent mycobacterial tuberculosis bacteria.[22] Clinicians need to keep tuberculosis in the differentials of malignant lesions, at least in endemic regions, in perplexing cases, and when the response to treatment deviates from the expected course.[23]

Also, TB can produce masses and nodes that can complicate staging of neoplastic diseases.[24]

This will help in better management of patients and prevent any fatality. Therefore, it is necessary to document presence of TB or caseating granulomas in histopathologic specimen of oncology patients with malignancy. However more elaborate studies are needed in Indian setting about the coexistence of TB and cancer.

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