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RESEARCH ARTICLE

ROLE OF TARGET THERAPY AND IMMUNOTHERAPY IN A RARE CASE OF CA COLON WITH LEFT SIDED KRUKENBERGS TUMOR AND BENIGN SPINDLE CELL TUMOR IN LEFT LUNG: A CASE REPORT

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ABSTRACT

Context: We are presenting a rare case of carcinoma colon (grade 4) with metastasis to left ovary (Krukenbergs) and benign spindle cell tumor in left lung diagnosed in a 65-year-old female. A brief literature review is presented. Patient was treated with CAPOX (Capecitabine and Oxyplatin) and Immunotherapy (Cetuximab). Surgical removal of left ovary and apparently no signs of cancer after 6 months of treatment. ***Inference:*** This case report highlights the potential benefit of combination of Target therapy and immunotherapy in the treatment of Krukenberg tumor. Although further studies are needed, immunotherapy could be considered as a treatment option in patients with Krukenberg tumor who have exhausted standard chemotherapy options. As our knowledge we report first case of simultaneously rare varieties of colon cancer and benign spindle cell tumor of lung. In a patient with history of malignancy, a benign mass should be diagnosed correctly with PET, core needle and IHC.

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INTRODUCTION

Patient: A 65-year-old female diagnosed with colon cancer with Krukenberg tumor and benign spindle cell tumor in left lung. Management: CAPOX (Capecitabine and Oxyplatin) and Immunotherapy (Cetuximab).

Outcome: Complete response

History: The patient is a 65-year-old female who presented with urinary infection and pain in left flank. The patient had a medical history of hypertension, diabetes and hyperlipidemia, and no family history of cancer. USG was done to rule out kidney stones ad incidental finding of Left ovarian mass, left pleural effusion. Initial investigations CECT scan and Immunoassay: HCG beta specific =0.75 (0-5.0), Alpha fetoprotein=2.73 (0-9.0), LDH=585 (<247), CEA=203.38 and CA-125=259.3 (0-35).

Diagnosis: Colonoscopy revealed a circumferential massin the hepatic flexure of colon, a biopsy of the colon mass (hepatic flexure) was performed and revealed a moderately differentiated adenocarcinoma, consistent with colon cancer. Next-generation sequencing demonstrated KRAS wild.

CT guided Trucut biopsy of lung mass, USG guided biopsy from adnexal mass were performed. Findings from Immunohistochemistry of lung tissue: positive for Vimentin, CD34, Bcl2, CD99, STAT6, Negative for CK, desmin, SMA, ER, Cd10, S100. (Favoring Benign mesenchymal Neoplasm-Solitary fibrous tumor). Immunohistochemistry of Ovarian mass: histopathological analysis: revealed a microscopic focus of metastatic adenocarcinoma in the left ovary. CDX positive, CEA, SAT B2, positive in neoplastic glands, CK 20 focal positive in neoplastic glands.CK7, PAX8,ER ,WT-1,negative in neoplastic glands.

Endometrial biopsy was normal. Omental biopsy normal with fibrofatty tissue features. Further investigations, including a PET/CT-scan showed a large multilobulated solid cystic mass lesion measuring (15.5x 11.3 cm)with FDG intake in solid areas in the abdominopelvic cavity predominantly on left side. Large non FGD avid heterogeneously enhancing low attenuation lobulated soft tissue mass lesion measuring (9.2x8.7cm) in posterior segment of left lung. On FGD avid soft tissue deposits along segment VI of liver, spleen, and multiple omental and peritoneal regions. A CT guided liver biopsy, adnexal mass, omental lymph nodes was performed confirmed the presence of metastatic disease in the ovaries, consistent with Krukenberg tumor and a benign spindle cell tumor in the left lung. Immunohistochemistry

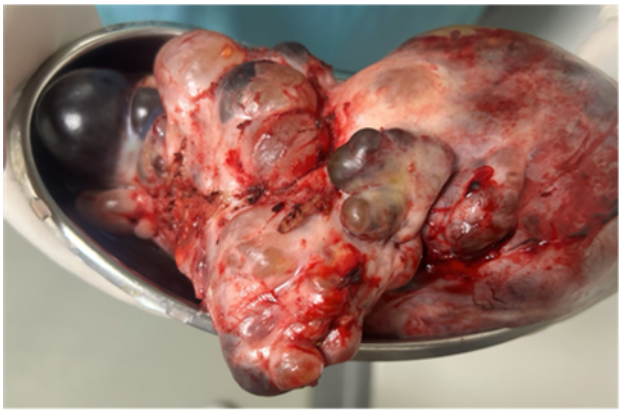

Fig. 1. Left ovary (Oophorectomy) specimen with necrosed areas (Krukenbergs Tumor

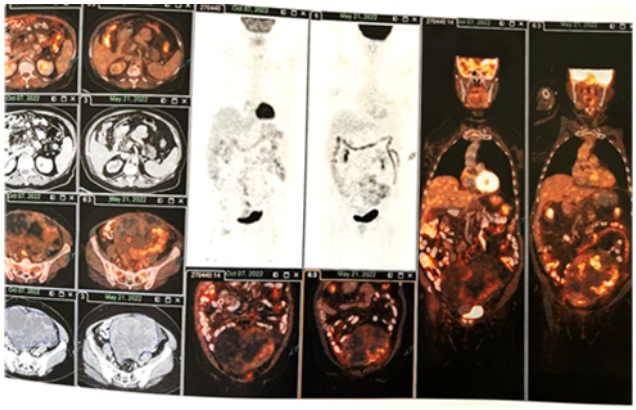

Fig. 2. PET scan scan before and after Target therapy and immunotherapy

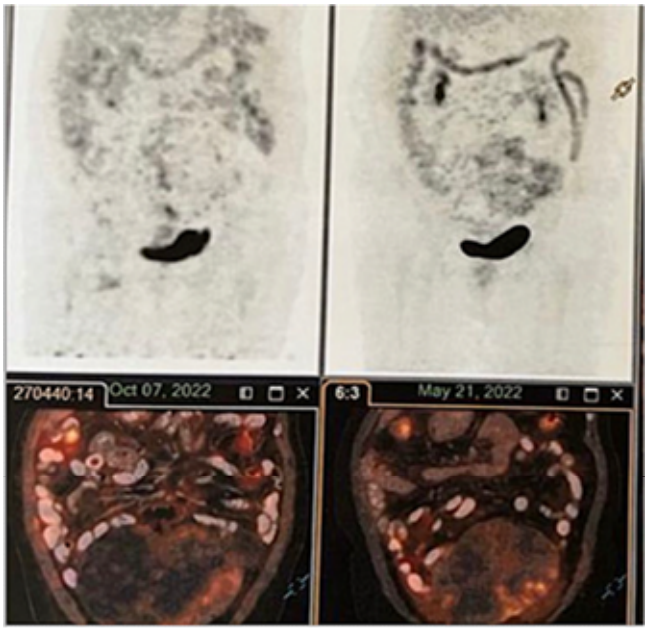

Fig. 3. PET scan comparing pre and post treatment changes

Treatment: The patient was started on first-line chemotherapy, which included CAPOX and Cetuximab. After 5 cycles of CAPOX and 6 cycles of Cetuximab, imaging studies showed stable disease in the left ovary.

Palliative chemotherapy: 5 courses of Cap Ox-Cetuximab. >resulted in decrease size of left ovarian mass (PET),CA125=17,CEA=13. >> no growth in colon and liver tumor decreased in first course and stabilized (PET)

Surgery: left sided oophorectomy with adhesidysis.

Additional investigation done for left ovary: Given the good response to combination of target therapy and immunotherapy,the patient was debulked by operated by oophorectomy.Grossly enlarged 25x15cm bosselated solid cystic left ovary with adhesions with omentum, sigmoid colon and small bowel was seen .no lymph nodes were seen. No ascites, liver, spleen normal, right ovary, and uterus normal.

Outcome: The patient received CAPOX 5 cycles and Cetuximab 6 cycles. The patient tolerated treatment well, with no significant adverse effects except for hand and feet skin reaction. The patient is asymptomatic from 6 months with normal levels of CEA and CA125 levels.

DISCUSSION

Adnexal masses are common and may present symptomatically or may be identified incidentally during imaging for another indication. The majority of adnexal masses are benign, but a small number will be invasive cancer (1).The most common presenting symptoms were abdominal pain, abdominal distention, ascites and abnormal uterine bleeding (7). Benign masses can be managed conservatively or with laparoscopy, avoiding unnecessary costs and morbidity. When malignancy is suspected, referral to a gynaecological oncologist is needed for proper staging and debulking surgery (2). However, surgical complications occurred in a minority of patients. This included anaemia, infections, intestinal obstruction, poor wound healing and cardiovascular related adverse events. Therefore, much research is aimed at discovering clinical, radiological and laboratory parameters that can be used to better determine the risk of malignancy in women presenting with an adnexal mass, so the patients receive optimal treatment (3).

Ultrasound (US) is the first-line imaging modality, allowing the characterization of most adnexal masses. MRI is indicated in the characterization of sonographically indeterminate masses, whereas CT is indicated for further staging of a suspected ovarian cancer on US (4). For characterization of an adnexal mass, the following US imaging features have been widely used: wall irregularity, thick septations (3mm), papillary projections, solid components, and large size (4cm) (5). Recently, the IOTA simple rules model has been introduced to preoperatively assess adnexal masses with US. Five sonographic imaging features, each defining the B (benign) and M (malignant) categories are used to distinguish between malignant and benign adnexal masses (6). Thus, in expert hands approximately 78-80% of complex adnexal masses can be diagnosed with US alone. Furthermore, a recent study by Zhang *et al.* reported approximately half of the patients who tested CA-125 had abnormally elevated level. Serum CA-125 is the most common tumor marker for ovarian cancer with low specificity and sensitivity (7). Clinically, increased levels of CA-125 up to several thousand times is relatively common in epithelial ovarian cancer, while it's not frequently observed in metastatic ovarian cancer. The absolute level of CA-125 may help to differentiate primary from metastatic ovarian cancer (8). Metastasis to the ovary from non gynecologic organs accounts for 9% of all ovarian malignancies, and the most common nongynecologic primary site of ovarian metastasis is the gastrointestinal tract(7). The most common primary malignancy site of patients with ovarian metastases was found to be colon carcinomas, followed by endometrium and breast carcinomas (9). Out of the total cases of colorectal carcinomas, only 40% metastasized bilaterally and the majority were unilateral(9). The left ovary was the most frequent metastasis site of left-sided colorectal carcinomas(9). Ovarian metastases could be the first manifestation presentation of metastatic colon cancer, where the patient may be presenting with non-specific symptoms, for example, abdominal discomfort and abnormal vaginal bleeding (10). Colorectal cancer is a leading cause of cancer-related morbidity and mortality, with mortality being most frequently caused by metastatic disease (11).

The survival and quality of life of individuals with metastatic colorectal cancer (mCRC) have improved with the development of biologics (12). The agents include anti-vascular endothelial growth factor (VEGF) (bevacizumab/aflibercept), anti-epidermal growth factor receptor (EGFR) antibodies (panitumumab/ cetuximab), and regorafenib (an oral multi-kinase inhibitor) (12). The main determinant in selecting a specific biologic agent for these patients was what is known as the Kirsten rat sarcoma (KRAS) mutation status of the tumor, with patients who lack the mutation (wild-type; KRAS wild-type (wt) tumors) being the appropriate candidates for anti-EGFR-based therapies like Cetuximab and Panitumumab (12). Solitary fibrous tumor, previously known as benign localized mesothelioma, are spindle cell growths of fibroblastic origin that arise from the pleura, and most of which are benign, but local recurrence has been observed in 10% to 15% of cases after resection. The solitary fibrous tumor of the pleura (SFTP) is a rare primary tumor that originates from mesenchymal cells in the areolar tissue subjacent to the mesothelial-lined pleura. Only about 800 cases have been reported in the medical literature and in more than half of these cases, the neoplasm presents as an asymptomatic mass, that is large and benign in 78% to 88% of patients (13). These tumors are rare and exhibit overlapping features with other mesenchymal tumors which poses as a considerable diagnostic difficulty. Histologic assessment, selective immunohistochemical and molecular tools are the key factors that can aid in the distinction among the tumors (14). The pleura is the most common site of origin, but SFTs arise in many other body organs and locations. 60% to 80% of intrathoracic SFTs arise in the visceral pleura with the parietal pleura being the second most common location. Occasionally, tumors may arise in the mediastinum, from the diaphragm, or within the lung parenchyma. [15] SFTs are large round to lobulated well-circumscribed tumors that vary in size. Most tumors arising from the visceral pleura are pedunculated and attached to the lung by a vascularized pedicle whilst other tumors have a broad-based sessile attachment. Rarely, SFTs may be multiple. (15) The histological features of SFTs are quite variable as noted before. Benign tumors comprise of bland, short, fibroblastlike spindle cells with ovoid nuclei, evenly distributed in a fibrocollagenous stroma. The most common histological pattern has been termed the "patternless pattern" of Stout, in which there is random dispersion of spindle cells and collagen bundles throughout the tumor. A storiform or hyalinized arrangement has also been noted (15).

A key point to note is that the nuclear proliferation marker Ki67 (MIB-1) has been found to be useful in discriminating benign from malignant SFTs, with benign lesions having a low proliferative index (0%-2%), while malignant lesions show 20%-40% nuclear positivity. One study revealed that the mean proliferative index for benign tumors was 7.27 versus 13.48 for malignant SFTs. P53 has also been advocated as a useful marker seen in a higher proportion of malignant than benign SFTs. [(15)] The mainstay of management includes complete en bloc surgical resection for both benign and malignant varieties of the tumor. Complete surgical resection with long term follow up is indicated even if the tumor is histologically benign because of the risk of recurrence and malignant transformation. Wedge resection of the lung is the preferred technique for pedunculted tumors attached to the visceral pleura whereas sessile tumors arising on the lung require a larger resection of the lung. Sessile tumors on the chest wall require wide local excision, along with chest wall resection because of their predilection for local recurrence. Benign SFTP has a high cure rate and an 8% local recurrence rate that is usually amenable to curative re-excision. Nevertheless, the overall long-term cure rate for all patients is 88% to 92%.

CONCLUSION

This case report highlights the potential benefit of combination of Target therapy and immunotherapy in the treatment of Krukenberg tumor. Although further studies are needed, immunotherapy could be considered as a treatment option in patients with Krukenberg tumor who have exhausted standard chemotherapy options.

As our knowledge we report first case of simultaneously rare varieties of colon cancer and benign spindle cell tumor of lung. In a patient with history of malignancy, a benign mass should be diagnosed correctly with PET,core needle and IHC.

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