MEDICAL EDUCATION SERIES

INCYTE

Issue: March 2018 BREAKTHROUGH NEWS FROM CYTECARE CANCER HOSPITALS

AIMED WITH PRECISION. TACKLED WITH EXPERIENCE.

Dear Doctor,

We are glad to present you the second edition of Incyte, the scientific newsletter from Cytecare Cancer Hospital.

With each domain of cancer care getting more intensive and complex every day, it is difficult to keep updated with the advancements in cancer management. We publish and present this newsletter with the aim to share some insights from the special cases that have been managed at Cytecare.

The first case in this edition is probably the first ever reported case of mixed adenoneuroendocarcinoma of cervix. While MANECs themselves are a group of rare cancers, the appearance of MANEC in cervix in this case makes it of special interest. With no clearly defined treatment regimens for such extremely rare cancer, the case was successfully managed with a comprehensive treatment plan at our facility.

The second case is of a 74-year-old man with advanced hepatocellular carcinoma with portal vein involvement, making him unfit for surgery. The patient though old, was in good health and performance status, hence only a palliative care seemed insufficient and we ought for an alternative treatment option, transarterial radioembolization.

The third case here highlights the benefits of having a multidisciplinary tumour board (MTB) in early diagnosis of cancer. In this case, the clinical diagnosis of basal cell carcinoma (due to skin lesions) and relapse of a carcinoma of cervix (due to vaginal spotting) were the primary suspects. However, MTB agreed to rule out potential sources of vaginal bleeding, which revealed a very early stage renal cell cancer.

We, at Cytecare, take pride in sharing these insights into the advanced cancer diagnosis and management approach we follow at Cytecare. Additionally, we also hope to create awareness about the relatively less common but more advanced approaches in the field of cancer diagnosis and management.

Suresh Ramu
Co-founder & CEO

MANAGEMENT OF CLINICALLY DISTINCT AND RARE CARCINOMA-HIGH-GRADE MIXED ADENONEUROENDOCRINE CARCINOMA OF THE CERVIX (MANEC)

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Abstract

Mixed adeno-neuroendocrine carcinoma (MANEC) is an extremely rare cancer type, with the literature restricted to case reports and series. Cervical MANEC is a further unusual presentation and has hardly been described earlier. Here, we present a case of a 55-year-old lady who presented with foul smelling vaginal discharge and urinary disturbances. Her cervical biopsy revealed a transitional cell carcinoma. After thorough investigations and interdisciplinary team consensus, a type III radical hysterectomy with bilateral pelvic lymph node dissection was performed. The histopathology of the excised tumour revealed mixed adeno and neuro endocrine carcinoma of the cervix with IHC supporting diagnosis, making it probably the first ever described MANEC of cervix. Adjuvant radiotherapy and chemotherapy were administered in view of the high risk histology to prevent further metastasis, as per the multi disciplinary tumour board decision.

History of Present Illness

A 55-year-old, postmenopausal lady (P3 L3, FTND, sterilised) presented with the complaints of occasional foul smelling vaginal discharge and urinary disturbances for the past few weeks. She was suggested to undergo a cervical punch biopsy by her gynaecologist. Reports of cervical biopsy confirmed the diagnosis of transitional cell carcinoma.

Later, CT scan, and MRI were done which revealed a 4x3.1x4 cm lesion, involving the cervix and lower uterus with diffusion restriction. There was no extra-cervical or parametrial invasion or significant pelvic or para-aortic lymphadenopathy. She was then referred to Cytecare Hospital for further management.

Medical History

She was a known hypertensive and is on anti-hypertensives daily. There was no relevant family history of breast or genital cancer.

Physical and Systemic Examination

- The patient was obese with ECOG performance score 0.
- No supraclavicular lymph node metastasis was noted.
- Abdomen was soft and no mass was felt.
- Speculum examination revealed hyperaemic cervix, with an ulcero-proliferative growth snugly seated at the distal endocervix with no ectocervical or vaginal involvement. Uterus was also noted to be bulky. Bilateral parametria were supple; bilateral adnexae and rectal mucosa were free.

Diagnosis

The patient was diagnosed with carcinoma of cervix-clinical stage 1B1/B2.

Management

As per the protocol, slides and blocks of the cervical biopsy were reviewed at our center by an oncopathologist who opined this condition as adenocarcinoma of cervix. Previous MRI and CT films were also reviewed which had been found to concur with the present clinical stage. Hence, it was decided to perform radical hysterectomy with bilateral pelvic lymph node dissection (BPLND).

Type 3 radical hysterectomy with BPLND under general and epidural anaesthesia was performed. The excised cervical tumour (Fig. 1 & 2) was found to

measure about 4.5x2x1.5 cm with 1.6 cm of vertical infiltration extending to endocervical canal/isthmus/LUS. There was no venous or lymphatic vascular space invasion. The tumour margins were free; with no attachments to vaginal cuff, ectocervix, endocervix, right and left parametrium, and right and left adnexae. However, the tumour had involved the endometrium and myometrium; a leiomyoma was also identified. No lymph node involvement was detected among the examined lymph nodes (28 right pelvic and 25 left pelvic lymph nodes).

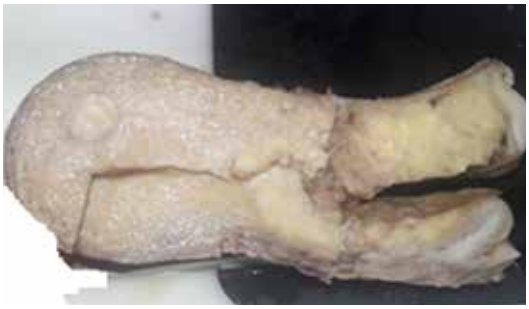


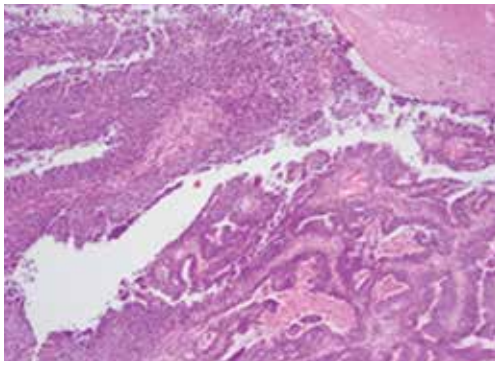
Fig. 1 & 2: Excised cervical tumour.

Patient had an uneventful peri-operative period. Urinary catheter was removed on 10th post-operative day and she was discharged on 5th post-operative day. Final histopathology report revealed mixed carcinoma of the cervix consisting of moderately differentiated adenocarcinoma component. There was another carcinoma component evaluated by immunohisto-chemistry (IHC).

Immunohistochemistry results of the excised tumour specimen.

Marker	Result
Synaptophysin	Negative
CEA	Focally positive in few glandular foci
p40	Negative
CD56	Negative
Ki 67 index	High index in all areas of differenti-ation
NSE	Negative
Chromogranin	Strongly and diffusely positive in all areas of differentiation
CK7	Weak and variable
HMWCK	Negative
p16INK4a	Strong positivity throughout the tumour

With the IHC results (Fig. 3 & 4), the cancer was identified as a small cell neuroendocrine carcinoma of the cervix. The p16INK4a positivity favours cervix primary and HPV association. Minor (30%) amphicrine component was identified (adeno-neuroendocrine differentiation) in the single block submitted for IHC.



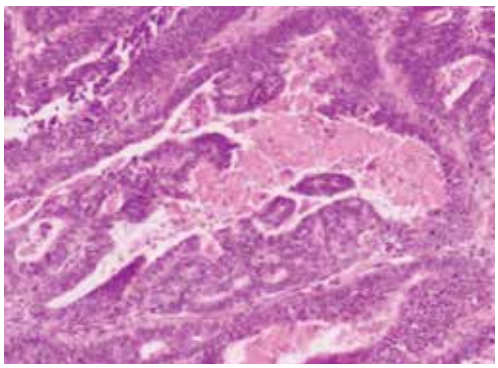


Fig. 3 & 4: IHC stain-Adeno-neuro-endocrine differentiation.

This case was discussed with the multi-disciplinary tumour board for further management. Considering the aggressive nature of the neuroendocrine component of MANEC, size, and stromal invasion criteria on HPE, a decision was taken to initiate adjuvant chemotherapy and radiotherapy (i.e. two cycles of Cisplatin + Etoposide, followed by external beam radiation therapy with weekly Cisplatin followed by two more cycles of Cisplatin + Etoposide and Brachytherapy).

The patient tolerated the treatment well, and is clinically well post 5 months of treatment. Regular follow-ups have been mandated.

Discussion

Neuroendocrine carcinomas are highly aggressive in nature and generally carries a poor prognosis. These rare carcinomas originate from the endodermal cells. Mixed adeno-neuroendocrine carcinoma (MANEC) is a further rare carcinoma, which results from the addition of a significant proportion of malignant exocrine glandular cells to the neuroendocrine carcinomas.[1]

In practice, MANEC comprises both exocrine and neuroendocrine components, with each component contributing to at least 30% of the tumour volume.[2,3]

MANEC originates from bidirectional differentiation of multi-potential stem cells. MANEC is further categorised into collision and composite types. In collision tumours, there are two separate but adjacent neoplasms, resulting from biclonal transformation of endocrine cells and exocrine cells in close contact. On the contrary, the composite or amphicrine tumours originate from multidirectional differentiation of a single neoplasm comprising of intermixed endocrine and exocrine cells.[1] In amphicrine tumours, both exocrine and neuroendocrine components are present within individual tumour cells and hence these lesions are unique.[1,2]

Definitive diagnosis of MANEC can be established based on the tumour architecture and specific neuroendocrine markers such as chromogranin, synaptophysin, CD56, and neuron-specific enolase (NSE). Additionally, markers on non-endocrine differentiation such as keratin 7 and keratin 20, CDX2, and carcinoembryonic antigen (CEA) are also investigated.[4]

Aggressive multidisciplinary oncologic management is warranted for MANEC. This involves well-selected surgical management, along with systemic with or without regional therapy, as required. Furthermore, considering the high risk of recurrences, regular follow ups and optimal management of relapses are also required.[3]

Most of the literature describes the occurrence of MANEC in the gastro-intestinal tract, pancreas, gallbladder, bile duct, ampulla and appendix.[1] Ludmir *et al.* in his publication (2016), mentioned that so far, only 24 potential cases of amphicrine carcinoma have been identified. According to their publication, only 14 cases of gastro-intestinal tract amphicrine carcinoma, five case reports in the stomach, six cases of liver amphicrine carcinoma, and two cases of hepatopancreatic ampulla amphicrine carcinoma have been identified.[2]

Another publication by Nishimura C, *et al.* (*Case Rep Oncol. 2013*), have also described a rare case of pancreatic metastasis prior to cervical MANEC, but not cervical MANEC *per se*.[5] Similarly, Fadiloglu *et al.* (*Turk J Obstet Gynecol. 2016*) have also reported a case of cervical adenoneuroendocrine carcinoma with ovarian metastasis.[6]

This case may probably be the only reported cervical MANEC of cervix (without metastasis) which was successfully and optimally managed at our facility.

CONCLUSION

We present an extremely rare and clinically distinct cervical MANEC case, wherein an optimal surgery was followed by an apt histopathological diagnosis that included immunohistochemical studies using pertinent markers. In view of presence of both neuroendocrine and exocrine components, adjuvant chemotherapy and radiotherapy were further administered. The patient is healthy and still doing well even a year after the surgery.

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A CASE REPORT
OF HEPATOCELLULAR CARCINOMA

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Abstract

Hepatocellular carcinoma (HCC) is among the most common causes of cancer-related mortality. We present a case of an elderly patient, who had mild abdominal discomfort. A mild jaundice was also detected on routine check-up. A thorough diagnostic work-up revealed advanced stage HCC, with portal vein involvement. Considering the advanced stage of HCC and involvement of the portal vein, surgical management was not feasible. However, for a patient with good overall health and performance status, only palliation was considered inadequate and hence, TARE was administered. Adjuvant sorafenib therapy was also initiated for further management.

Case Presentation

A 74-year-old man presented for consultation with symptoms of bowel discomfort and mild jaundice. He had been diagnosed with hepatocellular carcinoma (HCC) and was referred for further treatment.

History of Present Illness

The patient had mild abdominal discomfort for about two months. One month back, he underwent routine health check-up, during which mild jaundice was detected. Ultrasonography revealed a lesion in the liver. On further consultation with a hepatologist, a CT scan was conducted, on the basis of which he was diagnosed with HCC and was referred for further treatment.

Past Medical History

The patient was a known diabetic for 20 years, and was taking oral hypoglycaemic drugs. He had been a regular alcoholic, but had quit drinking 10 years back. There was no relevant family history.

General and Systemic Examination

The patient was well nourished and appeared healthy (biological age 60 years); with good performance status. Systemic examination did not reveal any abnormalities.

Investigations

- Among the noteworthy, results of blood examinations were high bilirubin (total: 1.6 mg/dL and direct: 0.9 mg/dL), albumin/globulin ratio (0.98), alanine aminotransferase (245 U/L), aspartate aminotransferase (211 U/L) and alkaline phosphatase (157 U/L). Also, prothrombin time was higher (17.9 seconds)
- A CT scan revealed multiple tumours in the right lobe, diffuse tumour in the left lobe and left portal vein tumour thrombus. Liver cirrhosis, and mild fluid in the abdomen were also noted.
- Markers for Hepatitis B and Hepatitis C were negative.

Diagnosis

The patient was diagnosed as a case of Child's A liver cirrhosis with advanced HCC with portal vein thrombosis.

Management

Since he had advanced stage tumour, involving the portal vein, his treatment options were limited to radioembolization or palliative care. Considering the general overall good health and performance status, he was offered transarterial radioembolization (TARE), to which he agreed. Since the patient had known allergy to contrast media, he was given pre-procedural prednisolone 50 mg one hour before the procedure. In the first step, Tc-99 was injected into the left and right hepatic artery through angiogram to assess the lung shunt. The gamma scan revealed the lung shunt to be 4%, which indicated that the patient was eligible for TARE. On the next day, the patient developed mild infection in the form of ascites and swelling in legs and abdomen. He was treated with antibiotics - levofloxacin 500 mg PO for 5 days and diuretics - lasix 20 mg OD PO for 5 days; and was put on high protein diet. Once the infection was controlled, the next step of TARE was planned. Since the patient had developed urticaria as allergic response to contrast media during the first step despite pre-procedural prednisolone, it was decided to offer appropriate premedications during the second step of the procedure. Hence, a 50 mg dose of oral prednisolone was given 13 hours,

7 hours and 1 hour before the procedure, followed by a dose of diphenhydramine 50 ml benadryl injection just before the procedure. In the next step, appropriate dosages of Yttrium 90 was injected into tumour in both right and left lobes of the liver, depending on the tumour volume. On the next day, a PET scan was conducted to ensure the accurate deposition of the radioactive material. After 10 days, the liver function tests were conducted, which were the same as preprocedural levels. Hence, sorafenib therapy was initiated for further management. A follow-up after 3 months was suggested to evaluate the impact of treatment on liver tumours and decide on further course of treatment.

Discussion

Hepatocellular carcinoma is the third most common cause of cancer-associated mortality worldwide.[1] It is the most frightening complication of liver cirrhosis, with about 60-97% cases of HCC being reported with a background of cirrhosis.[2] In India, the common risk factors include chronic HBV infection, chronic HCV infection, alcohol consumption, and alfatoxin exposure. Another important risk factor for HCC and associated mortality is diabetes mellitus.[3] In this case, the patient had two risk factors, alcohol consumption and co-existence of diabetes mellitus, which might have contributed to the development of liver cirrhosis and consequently HCC.

A study has reported that in India, 50% of patients had TNM 4 stage HCC at the time of diagnosis.[2] Since later stages at presentation tremendously limits the treatment option, early detection of HCC is crucial.[2] According to a retrospective cohort-control study in India, patients who underwent surveillance were more likely to be diagnosed with potentially curable or treatable BCLC Stage 0/A disease and Stage B/C disease respectively, than late Stage D disease (χ^2=0.0007). Consequently, patients who were diagnosed at an early stage was associated with longer survival after diagnosis (Stage 0/A: 15.6 ± 14.2 months vs. Stage B/C: 9.43 ± 19.7 months vs. Stage D: 5.59 ± 11.9 months; p = 0.0006).[1]

According to the consensus recommendations of the Indian National Association for Study of the Liver (INASL), **HCC surveillance can detect early tumours that are potentially amenable to treatment, hence, all patients at risk of developing HCC and who are eligible for HCC therapy are candidates for regular HCC surveillance**. The recommendations further state that patients with cirrhosis (Child's A, B or C cirrhosis) should be subjected to surveillance for HCC. Surveillance is also suggested in patients with chronic HBV and HCV infections. There is a consensus that six-monthly ultrasound of abdomen by experienced personnel should be performed for surveillance test.[3]

The choice of treatment in HCC depends on the cancer stage. In patients with advanced stage tumours, where other modes of treatment are not indicated, palliative therapy forms the mainstay of treatment. However, trans-arterial radioisotope therapy (TART; also known as TARE) with Yttrium 90 may be considered in some patients of advanced HCC with portal vein thrombosis and good liver function (Child A).[3] Since, this patient had good performance status and liver function, TARE was attempted.

CONCLUSION

We present a case of advanced stage HCC with early stage liver cirrhosis in an otherwise healthy elderly patient. Due to advanced stage of tumour and the portal vein involvement, the management options were limited to only palliation. However, considering the good overall health and performance status, our team decided to go beyond palliation, and attempted TARE, which was well-tolerated by the patient. Further management with adjuvant sorafenib therapy was also initiated.

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INSIGHTS FROM THE MULTIDISCIPLINARY TUMOUR BOARD: EARLY DETECTION OF AN UNEXPECTED CANCER

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Abstract

While early diagnosis of cancer is crucial, it is often missed due to lack of recognition of subtle or vague symptoms. In such cases, a thorough discussion among a multidisciplinary tumour board can be crucial to offer a diagnostic work-up plan for early cancer detection. Here, we present a case of a very old woman, who presented with a scalp lesion and occasional vaginal spotting. She had a history of carcinoma of cervix, which was treated 15 years back. The immediate clinical suspicions were basal cell carcinoma and potential recurrence of carcinoma of cervix. The case was discussed among the Cytecare multidisciplinary tumour board, where the potential underlying causes, including a renal pathology, were discussed. On the basis of diagnosis work-up recommended by the MTB, she was diagnosed with a basal cell carcinoma and a very early stage renal cell cancer, instead of a recurrence of cervical cancer.

History of Present Illness

An 89-year-old woman was presented with a 2.2 cm lesion in the right side of temporal region of the scalp for the past 2 years. There was some oozing from the lesion, but not accompanied by any pain or bleeding. The scalp lesion had been diagnosed as a skin ulcer elsewhere. She has also started noting vaginal spotting from last few weeks.

Medical History

The patient had a history of cervix cancer which had been diagnosed and treated 15 years ago. She was also undergoing therapy for depressive illness. The patient did not have hypertension/diabetes or any cardiac issues. She was not on any medications like ecosprin or clopidogrel. No allergies were reported.

Physical and Systemic Examination

- The patient appeared healthy and well-nourished (BMI: 28.2 kg/m^2; weight: 61 Kg, height: 147 cm).
- BP: 130/80 mmHg
- Respiration rate: 20 breaths/hour
- Pulse: 82/minute
- She had moles all over her body.
- Local examination:
  - There was an ulceroproliferative lesion 2x2 cm on the right temporal region of the scalp, which was firm and non-tender. There was no bleeding or pain on touching it. Also, no palpable nodes were observed.
  - There was a suspicious dark mole on the left cheek, no nodes palpable.
  - A flay mole on the scalp was also there, which had not been increasing in size for the past few years.

Suspected diagnosis and further investigations

On the basis of clinical examination, the patient was suspected to have basal cell carcinoma. Also, a suspicion towards the recurrence of cervix cancer was also raised. The case was discussed in the MTB at Cytecare. During the rigorous discussion, it was agreed to rule out other potential sources of vaginal bleeding, including a renal issue. Hence, several tests were conducted for a thorough examination. During the investigations, a PET scan revealed 3 cms X 3 cms lesion on the right kidney, indicative of a very early renal cell carcinoma at the lower pole of the kidney (Figures 1 and 2). Also, another PET scan showed no recurrent disease in cervix, which ruled out the possibility of relapse of the cervical cancer (Figure 3).

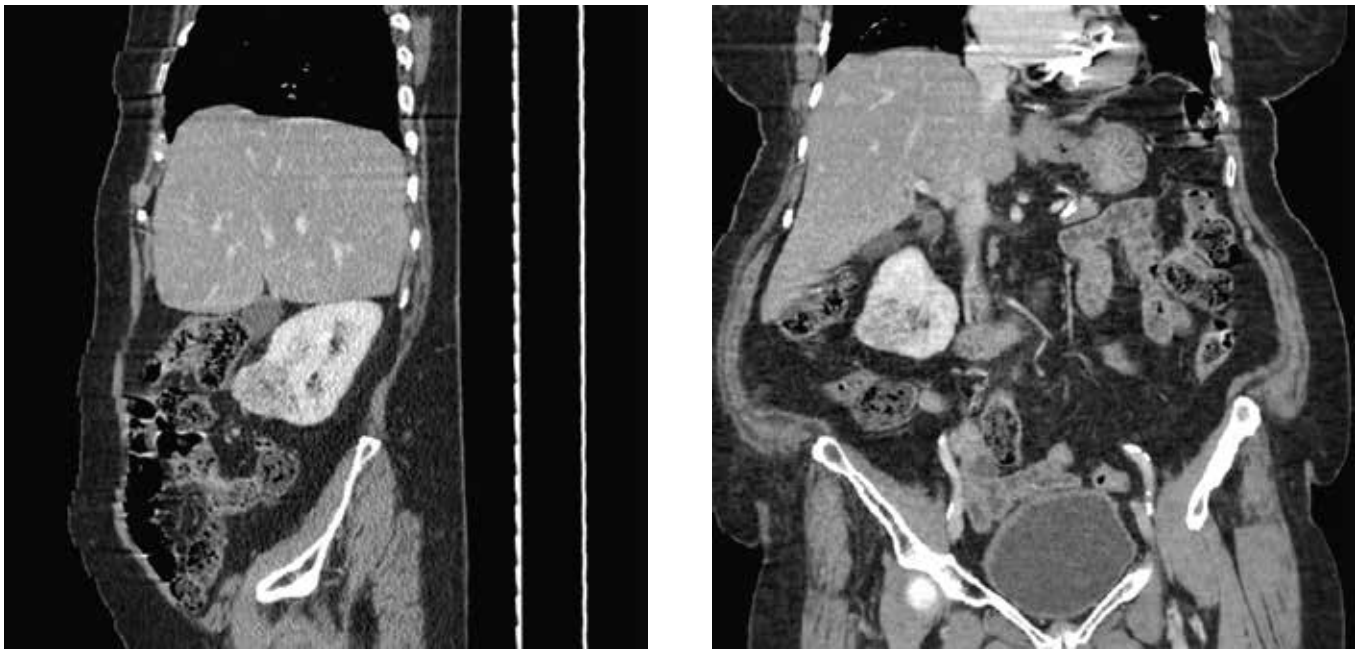

Figure 1: Lower pole renal mass (a) sagital view and (b) coronal view

Final diagnosis

On the basis of clinical findings, followed by tests, and scans, the patient was diagnosed to have basal cell carcinoma and a very early stage renal cell carcinoma. The patient has been advised for a nephrectomy and excision of the scalp lesion at the same sitting.

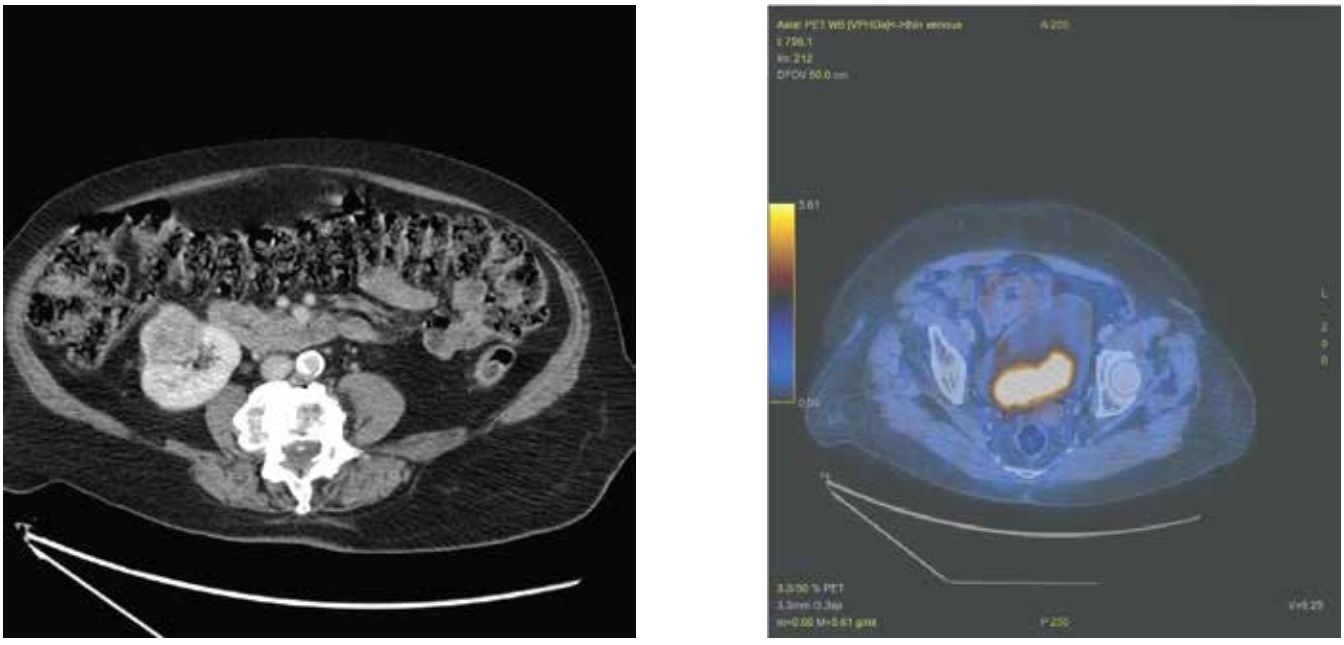

Figure 2: (a) Axial view of post-contrast image (b) 3D MIP of PET scan

Discussion

According to the WHO data, the cancer-related deaths in low- and middle-income countries exceed due to HIV/AIDS, tuberculosis and malaria, combined together. With such a vast impact on human and economic resources, the WHO has realized the need for early cancer detection as a part of cancer control programs.[1]

With the growing specialisation and complexity of cancer care, the need for a multidisciplinary approach with inputs from various specialists has been well recognised. Multidisciplinary tumour boards are forums

for multidisciplinary management of cancer patients, where a group of doctors from different specialties (medical oncologists, radiation oncologists, radiologists, pathologists, surgeons, and others) discuss the course of diagnostic work-up and management of cancer. During these meetings, clinical cases with laboratory, imaging, and pathological findings are presented. This is followed by discussion and debates from different perspectives of specialists. After this, group recommendations are made to achieve more accurate diagnosis and updated management plans. A study has reported that 35.6% of cases presented to the MTB were to get a diagnostic plan. Further, 17.1% cases were discussed to finalise pathology/radiology results.[2]

In the current case, there were suspicions regarding basal cell carcinoma and recurrence of carcinoma of cervix. However, during the MTB discussion, it was recommended to rule out other sources of vaginal bleeding. Hence, the group recommendations of additional diagnostic work-up helped to achieve the diagnosis of renal cell carcinoma at a very early stage.

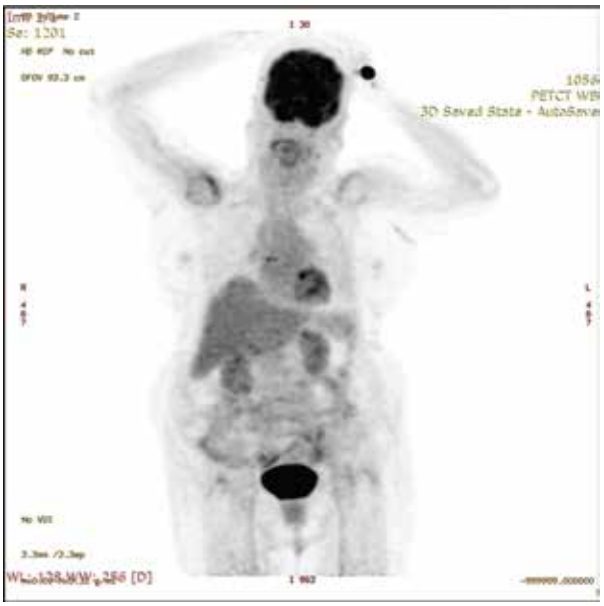

Figure 3: PET scan showing no recurrent disease in the cervix.

CONCLUSION

We present a case of an old woman, where the clinical suspicion of basal cell carcinoma and a recurrence of cervical cancer were raised, in view of the symptoms. However, with the diagnostic recommendations of the MTB, in addition to the confirmation of basal cell carcinoma, a very early stage renal cell carcinoma was detected.

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