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Adenocarcinoma admixed with neuroendocrine carcinoma of the cervix: A case report and review of literature

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ABSTRACT

A 40-year-old Ethiopian woman presented with a six-month history of non-foul-smelling whitish vaginal discharge. She also reported a one-year history of postcoital bleeding. A pelvic examination revealed a nodular, hard, and fragile cervical mass. In addition, there were nontender, firm nodules in the epigastric, periumbilical, gluteal areas, and thyroid gland. Investigations, including abdominopelvic ultrasound, magnetic resonance imaging, fine-needle aspiration cytology, and immunohistochemistry, confirmed mixed neuroendocrine carcinoma of the cervix with metastasis to the abdominal wall, gluteal area, lumbar vertebrae, and thyroid gland. The patient was started on palliative chemotherapy. Metastatic adenocarcinoma admixed with neuroendocrine carcinoma of the cervix presents a formidable disease phenotype, characterized by complex diagnostic and therapeutic obstacles. Multidisciplinary cooperation among oncologists, radiologists, pathologists, and surgeons is required to refine treatment approaches and improve patient prognoses for this uncommon and intricate malignancy.

1. Introduction

According to the latest statistics from the International Agency for Research on Cancer (IARC), cervical cancer is ranked as the fourth most prevalent cancer among women worldwide. In 2020 alone, there were 604,127 new cases reported, and sadly, 341,831 deaths were attributed to cervical cancer [1]. The primary causative agent for these types of cancers is the human papillomavirus (HPV), which is widely recognized as a significant contributor to the development of cervical neoplasms. While adenocarcinoma accounts for approximately 5% of cervical malignancies, neuroendocrine neoplasms (NEN) are relatively uncommon and represent less than 1% of all gynecological malignant tumors. Within this category, mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) are even rarer [2]. One specific type of MiNEN is known as adenocarcinoma admixed with neuroendocrine carcinoma of the cervix, previously known as mixed adenoneuroendocrine carcinoma, which is an extremely uncommon and aggressive tumor characterized by the simultaneous presence of both glandular and neuroendocrine components [3].

Adenocarcinoma admixed with neuroendocrine carcinoma of the cervix is characterized by abnormal vaginal bleeding, pelvic pain, or discharge. However, its clinical presentation can resemble that of more common cervical malignancies, leading to delays in accurate diagnosis. Early detection and prompt management are crucial due to its aggressive nature, in order to achieve optimal therapeutic outcomes [4,5]. Cervical small-cell neuroendocrine carcinoma combined with adenocarcinoma requires the presence of both neuroendocrine and non-neuroendocrine components, which may be separate or mixed. This combination is often difficult to identify [6]. Immunohistochemical staining for neuroendocrine markers is essential for confirming neuroendocrine differentiation [7]. The rarity and complex morphological features of this histological entity pose diagnostic and therapeutic challenges.

Abbreviations: CgA, chromogranin; CT, computed tomography; FNAC, fine-needle aspiration cytology; IARC, International Agency for Research on Cancer; MANEC, mixed adenoneuroendocrine carcinoma; MRI, magnetic resonance imaging; SWE, shear-wave elastography; Syp, synaptophysin; US, ultrasound.

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There is currently no consensus on the best treatment approach for adenocarcinoma admixed with neuroendocrine carcinoma of the cervix due to its rarity. Current management typically involves a multidisciplinary approach, including surgery, chemotherapy, and radiation therapy. Here, a case is presented of adenocarcinoma admixed with neuroendocrine carcinoma of the cervix with multiple metastases to the skin, lumbar vertebrae, and thyroid gland in a 40-year-old woman.

2. Case Presentation

A 40-year-old Ethiopian woman presented with a six-month history of non-foul-smelling, whitish vaginal discharge. Initially, the discharge was serous in nature but later became whitish. Alongside this, she reported significant weight loss, anorexia, and loss of appetite, all of which had persisted for the same duration. Additionally, she experienced abdominal wall and gluteal swelling. The patient also reported a history of postcoital bleeding for the past year, although she denied having multiple sexual partners. There was no personal or family history of diabetes, hypertension, asthma, or any known drug allergies. Furthermore, she tested negative for retroviral infection.

Upon examination, the patient presented with a chronically sick appearance, characterized by severe emaciation. However, her vital signs fell within the normal range. Notably, her conjunctiva appeared pink, and her sclera showed no signs of icterus. There were no clinically significant palpable lymph nodes in the neck, axillary, or groin regions. Nevertheless, a non-tender thyroid enlargement measuring 3*2 cm was observed. The patient's chest examination revealed clear and resonant sounds. Abdominal examination indicated the presence of palpable, nontender, firm nodules in the epigastric and periumbilical areas. No signs of fluid collection or organ enlargement were noted.

Regarding the genitourinary system, there was no tenderness in the suprapubic or costovertebral angle regions. However, a pelvic examination revealed a nodular, hard, and easily fragile cervical mass, with evidence of blood on the examining finger. Additionally, a firm, nontender gluteal swelling measuring 4*3 cm was observed.

The patient's renal function test, liver function test, serum electrolytes, and complete blood count all fell within the normal range. A chest x-ray did not reveal any abnormalities. However, the abdominal ultrasound showed a significant solid mass with minimal internal color Doppler flow located near the cervix, measuring 6*6 cm. The surrounding structures did not appear to be involved. Additionally, two large oval-shaped masses with heterogeneous echotexture and multiple cystic components were observed in the anterior abdominal wall muscles around the umbilicus. Other internal organs appeared to be normal. Based on these findings, the primary focus was on the cervical mass, likely indicating cervical cancer, and the presence of abdominal wall deposits.

On pelvic MRI, a relatively ill-defined mass measuring 5.2*6.3*6.5 cm was observed originating from the anterior cervix (Fig. 1). The mass exhibited T1 low signal and T2 high signal, diffusion restriction, and post-contrast avid enhancement. It extended to involve the upper two-thirds of the vaginal wall, predominantly anteriorly. Parametrial invasion and right adnexal invasion were present, but there was no clear invasion of the urinary bladder or rectum. Multiple pelvic lymph nodes of different sizes were detected in the region of the bilateral internal iliac group, with the largest measuring 2.1 cm, in the right internal iliac group. A small amount of pelvic peritoneal fluid signal collection was also noted. Additionally, there were masses and nodules of varying sizes involving the subcutaneous tissue on the lower back, gluteal area, and anterior abdominal wall (Fig. 2). These lesions exhibited similar signal intensity in all sequences and showed similar post-contrast enhancement as the cervical mass. Furthermore, a similar lesion was observed involving the pedicle and transverse process of the L5 vertebrae on the left side (Fig. 3).

The cervical biopsy revealed a predominantly ulcerated surface with a focal endocervical lining composed of diffuse discohesive sheets and perivascular proliferation of intermediate-sized cells. These cells exhibited nuclear molding, one to multiple small nucleoli, brisk mitotic activity, numerous apoptotic bodies, areas of necrosis, and numerous interspersed tingible body macrophages, giving rise to a 'starry sky' appearance. These findings indicate a high-grade malignancy with a differential diagnosis that included non-Hodgkin's lymphoma, alveolar rhabdomyosarcoma or Ewing sarcoma. Therefore, immunohistochemistry was ordered to confirm the diagnosis (Figs. 4–9).

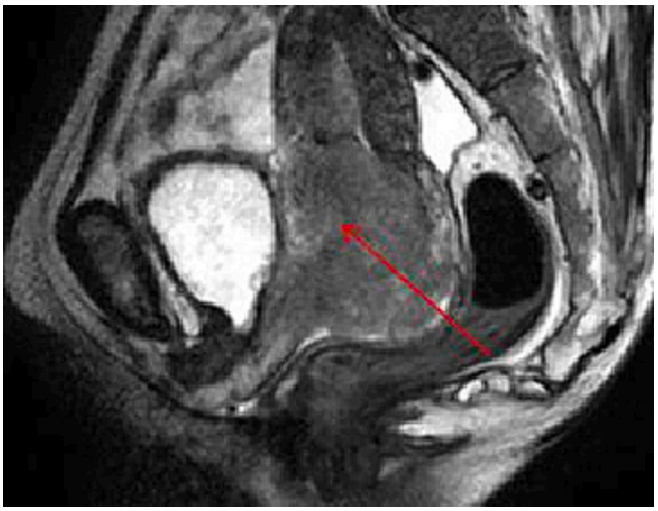

Fig. 1. Pelvic MRI showing a relatively ill-defined mass measuring 5.2*6.3*6.5 cm originating from the anterior cervix.

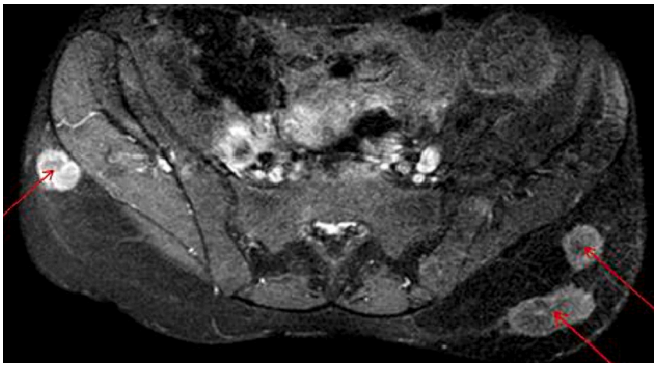

Fig. 2. Pelvic MRI showing multiple metastatic gluteal nodules.

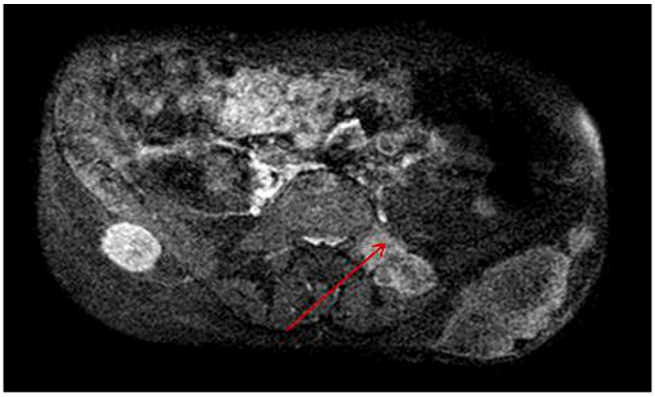

Fig. 3. Pelvic MRI showing a nodule involving the pedicle and transverse process of the L5 vertebrae on the left side.

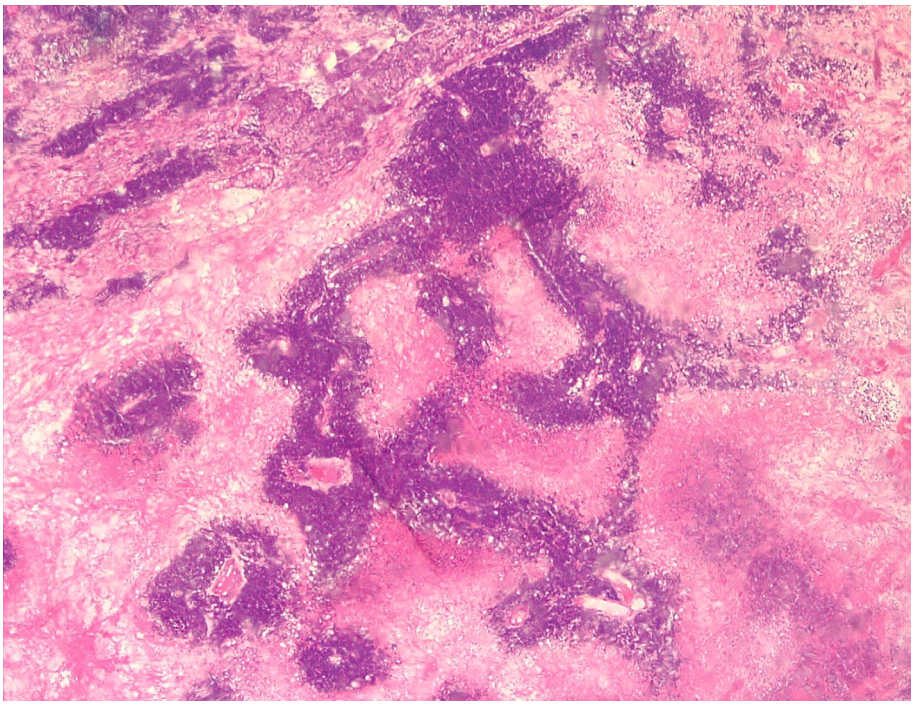

Fig. 4. Biopsy from the cervical mass showing neuroendocrine component with large area of necrosis (low power).

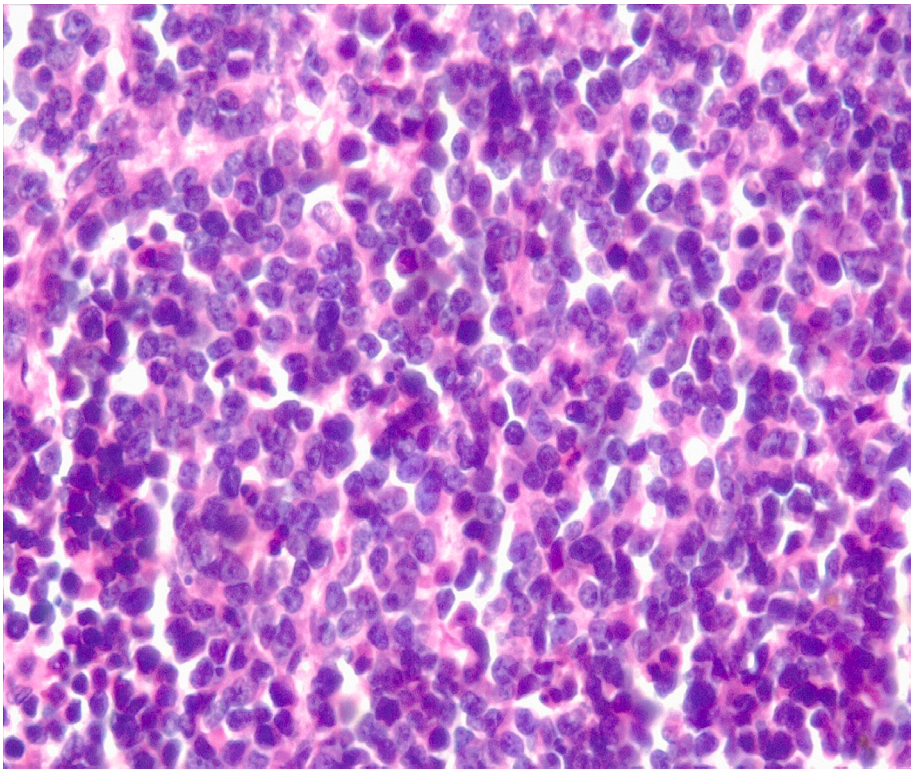

Fig. 5. Biopsy from the cervical mass showing neuroendocrine component with monomorphic round cells with open chromatin and conspicuous nucleoli (high power).

Subsequent immunohistochemistry analysis showed a diffuse proliferation of hyperchromatic cells that tested positive for synaptophysin and chromogranin. Additionally, solid nests with occasional gland formation were positive for pancytokeratin. Both groups, however, tested negative for CD 45. This indicates a mixed adenocarcinoma with neuroendocrine carcinoma (it was not possible to classify it further into HPV-associated or HPV-dependent adenocarcinoma).

Fine-needle aspiration cytology (FNAC) examinations of the abdominal wall and buttock revealed fibrofatty tissue that had been infiltrated by intermediate to large round cells. These cells exhibited clear cytoplasm and were mixed with smaller, round cells that possessed compact chromatin. Additionally, a few scattered large cells were

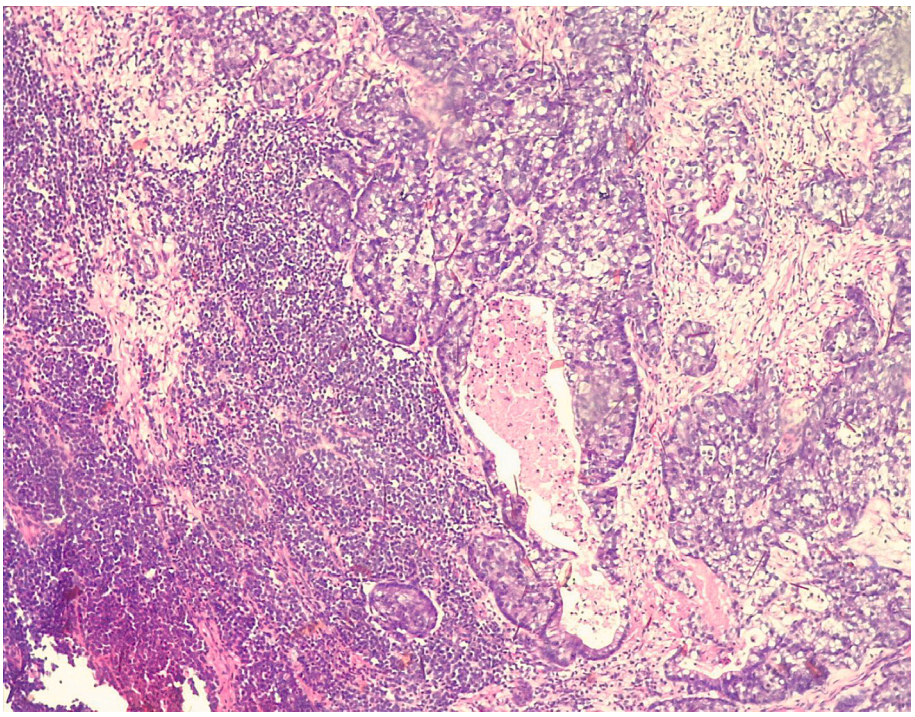

Fig. 6. Biopsy from the cervical mass showing mixture of the solid sheets of neuroendocrine component on the left and the nested epithelial adenocarcinoma with abundant clear cytoplasm on the right.

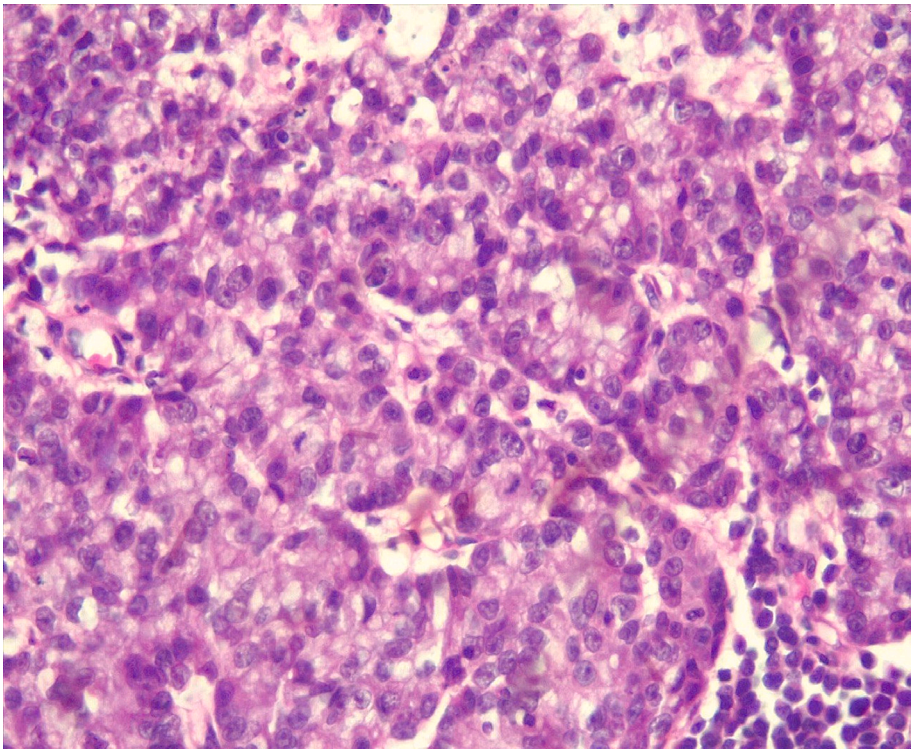

Fig. 7. Biopsy from the cervical mass showing the epithelial clusters of the adenocarcinoma component with abundant foamy cytoplasm having two mitotic figures in the center.

observed, displaying a moderate amount of rhabdoid cytoplasm. Foci of necrosis were also present, indicating the presence of malignant small round cells (Figs. 10–12). Moreover, FNAC of the thyroid gland demonstrated the presence of discohesive sheets of round to oval cells. These cells exhibited coarse chromatin and were found in a background of colloid and necrotic material, suggesting the likelihood of metastasis (Figs. 13 and 14).

Hence, following the confirmation of stage IV adenocarcinoma admixed with neuroendocrine carcinoma of the cervix, with metastasis to various areas, including the skin (abdominal wall, gluteal area),

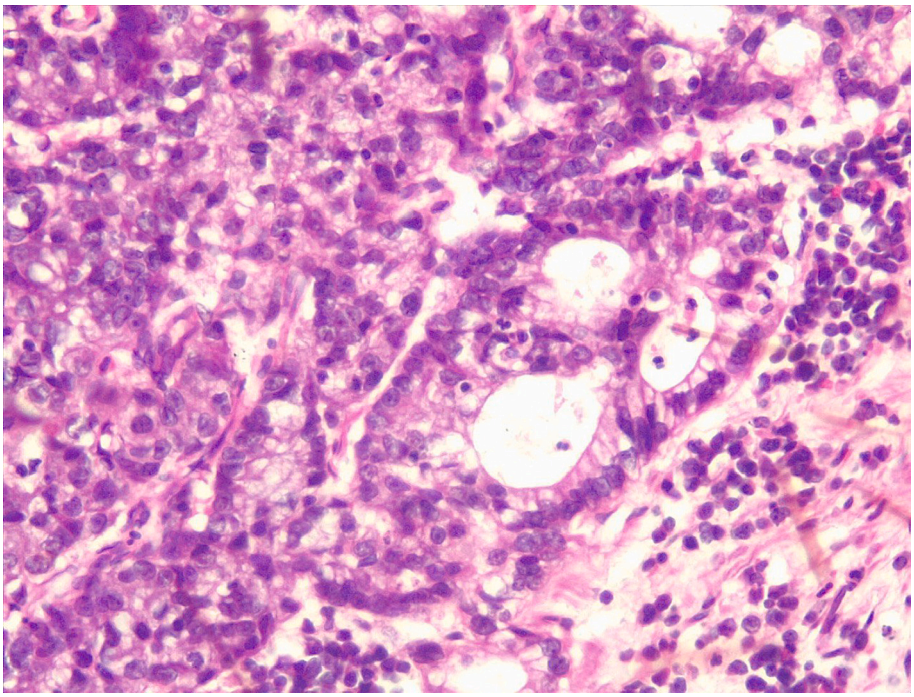

Fig. 8. Biopsy from the cervical mass showing the epithelial clusters of the adenocarcinoma component with abundant foamy cytoplasm forming cribriform like glandular lumen with smooth borders.

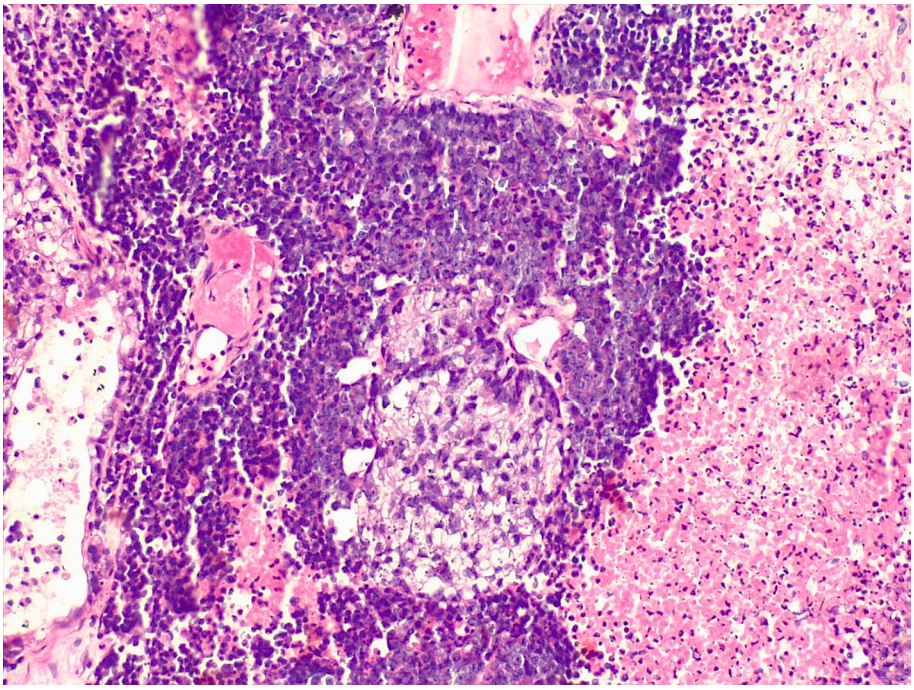

Fig. 9. Biopsy from the cervical mass showing neuroendocrine component with sheets of monomorphic round cells with 'salt and pepper' chromatin above and below to a central tight cluster of epithelial cells with abundant foamy cytoplasm (adenocarcinoma component).

lumbar vertebarae transverse process, and thyroid gland, the patient's treatment plan commenced with palliative chemotherapy. Specifically, she began receiving etoposide at a dosage of 130 mg/m^2 and cisplatin at a dosage of 45 mg/m^2. Additionally, the patient was administered tramadol intravenously twice a day at a dose of 100 mg, bisacodyl orally once daily at a strength of 10 mg, and cimetidine intravenously as a single dose of 400 mg. The patient was undergoing chemotherapy at the time of writing.

3. Discussion

Cervical cancer is a significant cause of death among women globally, ranking fourth after breast, lung, and colon cancer. It poses a major public health concern [8]. Adenocarcinoma admixed with neuroendocrine carcinoma of the cervix is an uncommon cancer with a bleak prognosis. As per the World Health Organization's classification, adenocarcinoma admixed with neuroendocrine carcinoma of the cervix

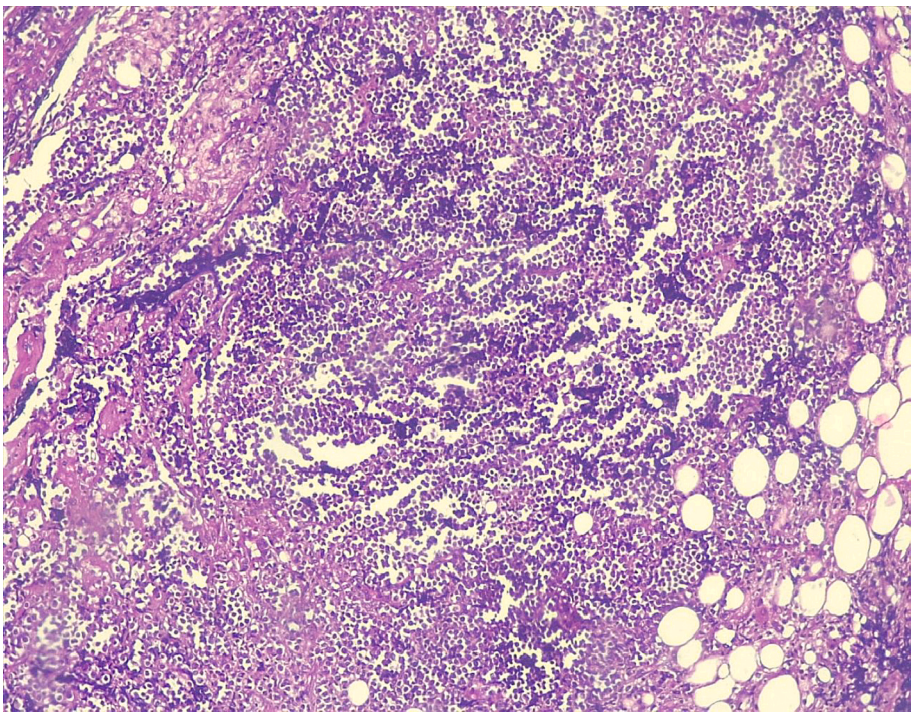

Fig. 10. Biopsy from the gluteal nodule showing similar monomorphic round cells with open chromatin and conspicuous nucleoli similar with the neuroendocrine component from the cervix (low power).

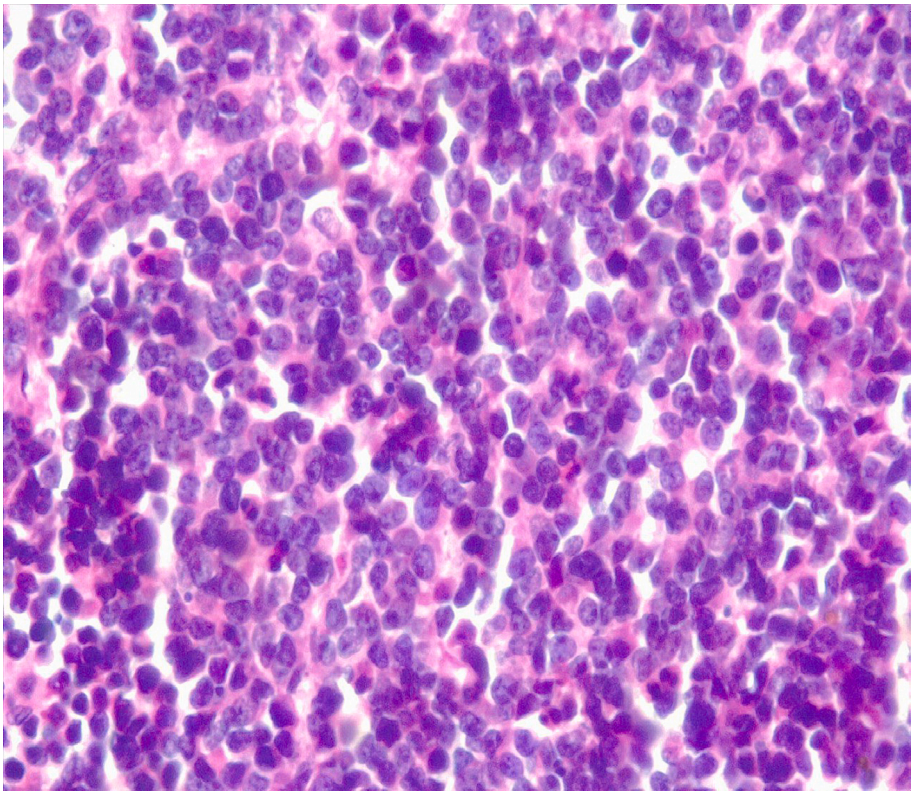

Fig. 11. Biopsy from the gluteal nodule showing sheets of monomorphic round to oval cells with conspicuous to prominent nucleoli (high power).

is characterized by a combination of adenocarcinoma and neuroendocrine carcinoma, with each component comprising more than 30% of the tumor cells [4,5]. Limited research exists on adenocarcinoma admixed with neuroendocrine carcinoma, with most studies consisting of small-scale investigations and individual case reports. Clinical manifestations of the small-cell-type neuroendocrine carcinoma bear similarities to those of low-grade neuroendocrine tumors, such as vaginal bleeding and the presence of an exophytic mass in the cervix. The median age of

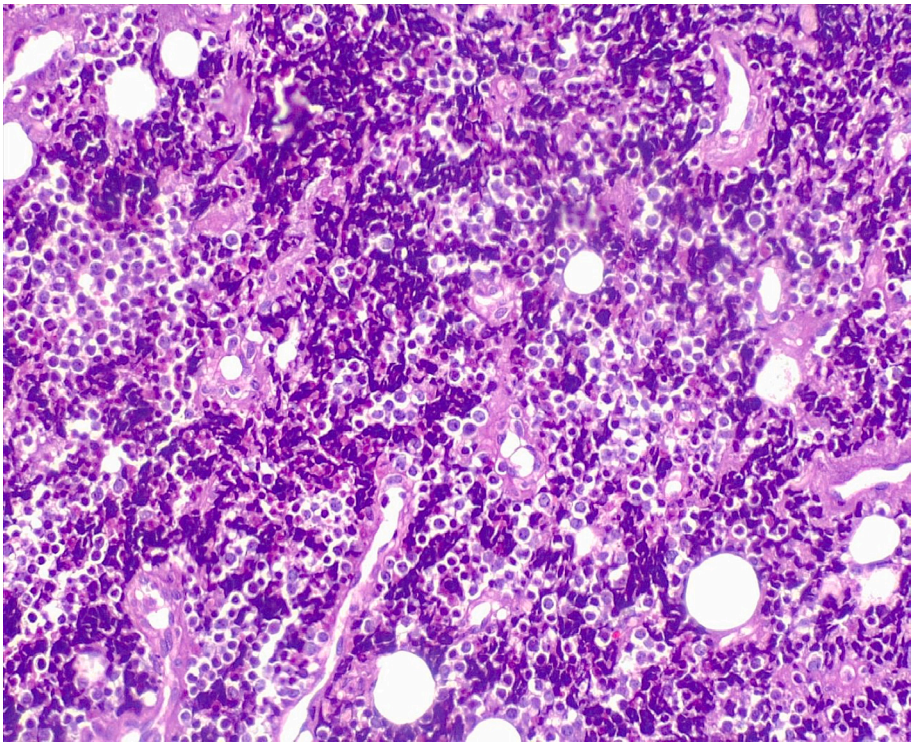

Fig. 12. FNAC from the umbilical nodule showing similar monomorphic round cells with open chromatin and conspicuous nucleoli similar with the neuroendocrine component from the cervix.

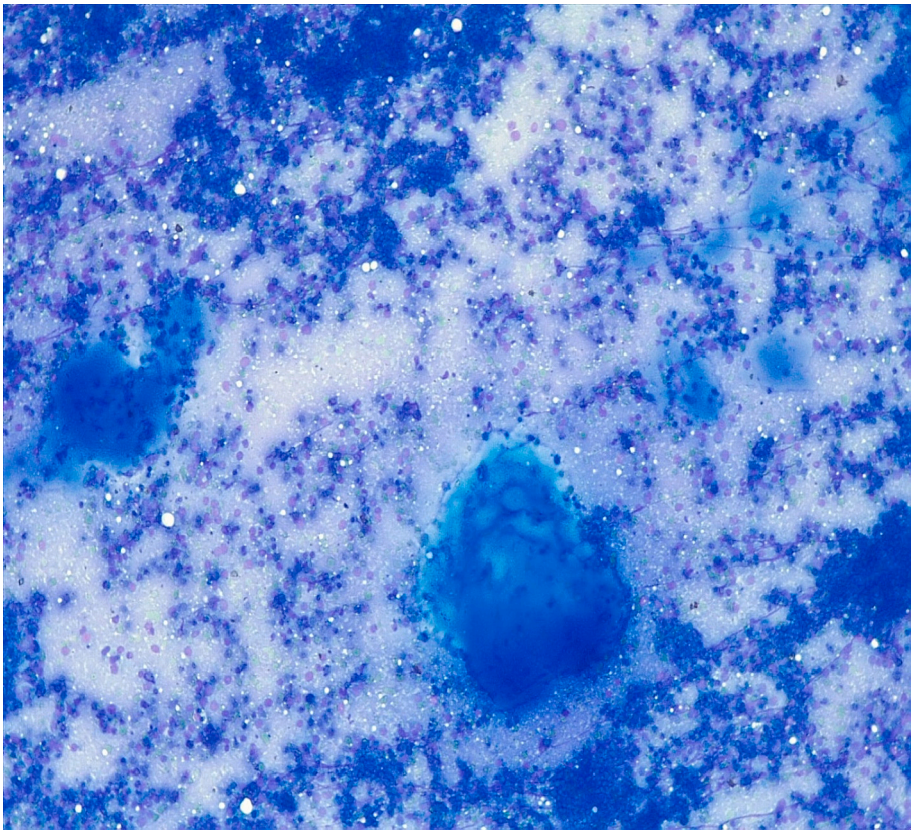

Fig. 13. FNAC from the thyroid nodule showing discohesive sheets of round to oval cells with course chromatin in colloid and necrotic background (20×).

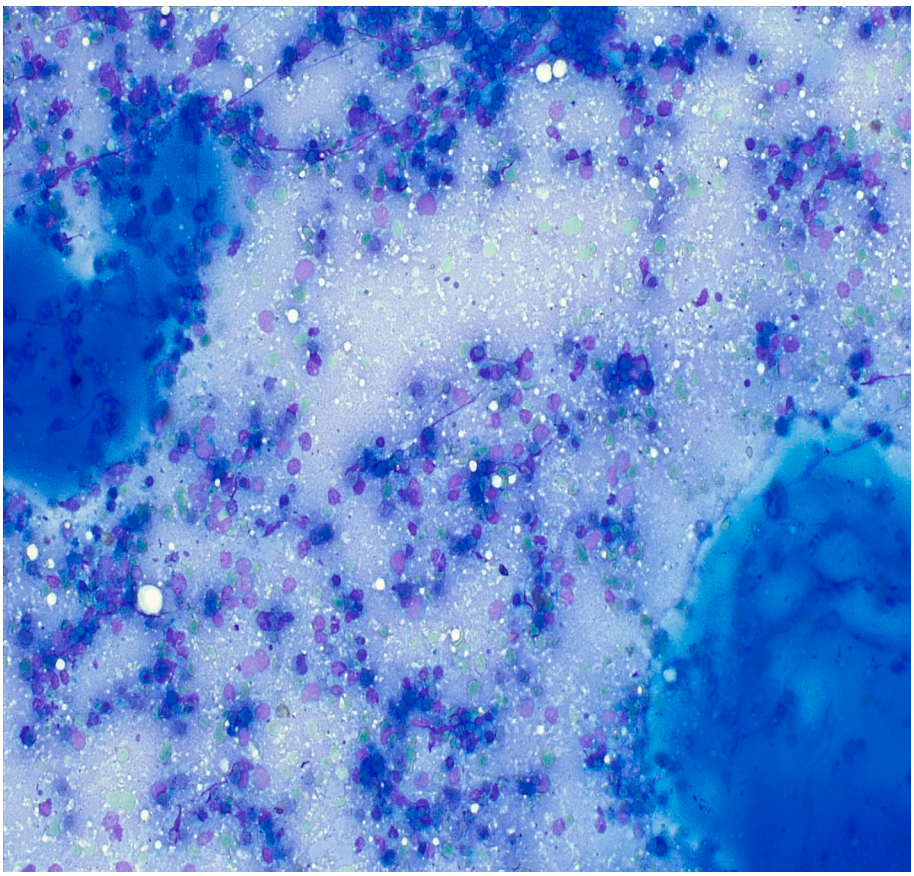

Fig. 14. FNAC from the thyroid nodule showing discohesive sheets of round to oval cells with course chromatin in colloid and necrotic background (40×).

patients affected by this condition is 44 years, ranging from 34 to 75 years [9]. The present patient was a 40-year-old woman who presented with vaginal discharge, post-coital bleeding, and an exophytic mass on examination.

It is important to note that a suitable radiological examination is crucial for aiding in the clinical diagnosis and determining the size or extent of this tumor before surgery. The International Federation of Gynecology and Obstetrics (FIGO) approves a clinical examination that includes various procedures such as rectovaginal examination, chest radiograph, intravenous pyelogram, cystoscopy, and proctoscopy. However, physicians tend to rely on advanced radiological imaging studies like computed tomography (CT) and magnetic resonance imaging (MRI) instead of solely relying on clinical examinations and basic imaging techniques. In addition to the standard diagnostic procedures, this patient underwent MRI scanning due to its advanced capabilities in examining pelvic organs and structures beyond the pelvic area. This cutting-edge technology enabled us to thoroughly assess the mass and its extent of spread with exceptional clarity.

The diagnosis of adenocarcinoma admixed with neuroendocrine carcinoma of the cervix requires a combination of clinical, histopathological, and immunohistochemical evaluations. Advanced imaging modalities like MRI and positron emission tomography-computed tomography (PET-CT) can assist in staging the disease and planning the appropriate treatment. Furthermore, molecular testing for specific genetic alterations may offer valuable prognostic information [10]. The patient underwent a comprehensive assessment, including a clinical examination, histopathologic analysis, and immunohistochemistry evaluation.

Markers used for immunohistochemical detection of neuroendocrine differentiation in small-cell cases include chromogranin (CgA), synaptophysin (Syp), and the cell proliferation index (Ki-67). Research on chromogranin primarily focuses on neuroendocrine tumors. According to a study, chromogranin A (CgA) is an acidic glycoprotein and a member of the granin family. It is exclusively found in dense core granules and serves as a storage site for peptide and catecholamine hormones in endocrine organs and neuroendocrine cells. CgA is a valuable tumor marker, although it does have its limitations. Increased levels of CgA are observed in neuroendocrine tumors due to heightened secretion activity. Additionally, CgA levels can significantly increase in tumor cells that have metastasized compared to those that are still localized at the original site [7]. The employed CgA and synaptophysin as markers to evaluate the neuroendocrine differentiation, and both of these markers yielded positive results. Additionally, pancytokeratin was utilized to assess the presence of the glandular component, and it also yielded a positive outcome.

The primary pathways through which cervical cancer spreads to other parts of the body are direct local extension and lymphatic metastasis. The most frequently affected sites of metastasis include the vagina, parametrium, and pelvic lymph nodes. While distant hematogenous metastases are not common, they can occur in organs such as the pancreas, lungs, and bones [10,11]. Two hypotheses have been proposed to explain this phenomenon. Firstly, the high concentration of iodine and oxygen saturation in thyroid tissue may hinder the growth of malignant cells. Secondly, the high-velocity arterial blood flow in the thyroid may prevent the adhesion and implantation of malignant cells. However, it is important to emphasize that the occurrence of cervical cancer metastasizing to the thyroid is extremely rare [12,13]. To the best of our current understanding, few case reports document patients with adenocarcinoma admixed with neuroendocrine carcinoma of the cervix with thyroid metastasis.

Thyroid metastasis can be challenging to diagnose as it often does not show any symptoms and can be indistinguishable from primary tumors.

However, studies have shown that most patients with thyroid metastasis experience new or growing thyroid nodules, dysphagia, neck swelling, hoarse voice, and cough [14]. This patient did not have any symptoms other than swelling. Ultrasonography is the most effective diagnostic method for the thyroid gland, although it does not have specific features to diagnose thyroid metastases. Typical ultrasonographic appearances of metastases in the thyroid gland include a lack of clear boundaries and intra-nodular vascularization [12].

A new non-invasive diagnostic tool called two-dimensional shear-wave elastography (SWE) has shown promise in evaluating thyroid nodules. SWE provides simultaneous anatomic B-mode US imaging, allowing for more accurate assessments. Several studies have reported positive results when combining SWE with B-mode US in evaluating thyroid nodules, with benign nodules showing higher elasticity than malignant ones [15]. One study found that the majority of patients with non-thyroid metastases had normal thyroid function (87.6%). However, hypothyroidism may be associated with extensive infiltration of tumor cells [16]. While in the present case no thyroid function test was done to rule out hypothyroidism, the patient exhibited no symptoms indicative of hypothyroidism.

There exist divergent viewpoints concerning the use of surgical procedures for patients with metastatic thyroid tumors. Although no significant disparities in survival rates have been observed between subtotal and total thyroidectomy, a review suggests that total thyroidectomy is advisable for patients with small, multiple, bilateral nodules to prevent tumor recurrence [17]. Furthermore, another review indicates that patients who undergo thyroid lobectomy experience minimal tumor recurrence when the surgical tumor tissue margins are negative. Consequently, there is no notable discrepancy in survival rates and prognosis between subtotal and total thyroidectomy [18]. A surgical procedure for the thyroid metastasis was deferred due to the absence of any pressure symptoms in the patient and the presence of multiple other metastases. Consequently, the decision was made to proceed with chemotherapy.

Given its rarity, there is no consensus on the most optimal treatment approach for adenocarcinoma admixed with neuroendocrine carcinoma of the cervix. Presently, management typically involves a multidisciplinary strategy that combines surgery, chemotherapy, and radiation therapy. However, the effectiveness of different treatment modalities remains uncertain, underscoring the necessity for collaborative endeavors and prospective clinical trials to establish guidelines based on evidence.

4. Conclusion

Adenocarcinoma admixed with neuroendocrine carcinoma of the cervix is an exceptionally uncommon and highly aggressive form of cancer that presents significant difficulties in both diagnosis and treatment. To fully comprehend the molecular mechanisms that drive this malignancy, additional research is imperative. It is also crucial to refine diagnostic techniques and establish effective treatment approaches. The collaboration between clinicians, pathologists, and researchers is of utmost importance in order to enhance the knowledge of adenocarcinoma admixed with neuroendocrine carcinoma and ultimately improve patient outcomes in this complex disease.

Contributors

Yohannis Derbew Molla wrote the original draft, was involved in the management of the patient, revised and submitted the figures.

Hirut Tesfahun Alemu contributed to the conception of the case report and patient care, and drafted the manuscript.

Almaz Enku Selamawi contributed to patient care and the literature review, and revised the article critically for important intellectual content.

Amare Yeshitla Tesema contributed to patient care and the literature review, and revised the article critically for important intellectual content.

Isak Omer Answar contributed to patient care and the literature review, and revised the article critically for important intellectual content.

Amanuel Kassa Tadesse contributed to the literature review, and critically revised the paper.

All authors approved the final manuscript.

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Patient consent

Written informed consent was obtained from the patient for publication of the case report and accompanying images.

Provenance and peer review

This article was not commissioned and was peer reviewed.

Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

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