Italian Journal of
Gynæcology & Obstetrics
June 2025 - Vol. 37 - N. 2 - Quarterly - ISSN 2385 – 0868

"Silent" HPV-associated cervical cancer – isolated cerebellar metastasis as unusual sign of cervical adenocarcinoma: a case report and literature review

Marco **Cerbone** [1], Anna **Aquilino** [1,*], Maria **Bardi** [1], Marta **Mele** [1], Arianna **Galante** [1], Maria **Bentivoglio** [1], Miriam **Dellino** [1], Antonella **Vimercati** [1,2], Gennaro **Cormio** [2,3], Ettore **Cicinelli** [1,2], Marco **Marinaccio** [1,2]

[1] Obstetrics and Gynaecology Unit, Department of Biomedical Sciences and Human Oncology, University of Bari "Aldo Moro", Bari, Italy.
[2] Interdisciplinar Department of Medicine, University of Bari, Bari, Italy.
[3] Gynecologic Oncology Unit, IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy.

ARTICLE INFO

History
Received: 15 May 2024
Received in revised form: 19 September 2024
Accepted: 06 November 2024
Available online: 30 June 2025

DOI: 10.36129/jog.2024.194

Key words
Cervical carcinoma; human papilloma virus; central nervous system metastasis; endocranic hypertension; atypical symptomatology.

***Corresponding author:** Anna **Aquilino**, M.D. Obstetrics and Gynaecology Unit, Department of Biomedical Sciences and Human Oncology, University of Bari "Aldo Moro", piazza Giulio Cesare 11, 70124, Bari, Italy.
Email: anna.aquiliino93@gmail.com.
ORCID: 0009-0000-9477-1778.

ABSTRACT

Background. This report focuses on an unusual case of primary central nervous system metastasis (CNS) from gynaecological cancer, specifically endocervical carcinoma, which typically occurs as part of a disseminated disease. Brain metastases from cervical cancer are rare, occurring in only 2% of cases. We reported data from hospital registry and the available literature with using the PRISMA methodology.

Case presentation. The patient, a 48-year-old woman without relevant medical history or gynaecological symptoms, went to the Emergency Room with progressive neurological symptoms. Imaging revealed obstructive hydrocephalus due to a mass in the IV ventricle, later identified as a cerebellar metastasis. Despite negative routine cervical screening, subsequent examinations revealed advanced cervical cancer with aggressive histology. The patient's poor performance status precluded standard treatments, so she underwent palliative care. Unfortunately, she succumbed to the disease after eight months.

Conclusions. This case underscores the ability of certain cancers, like HPV-associated adenocarcinoma of endocervical origin, to spread to distant organs without causing gynaecological typical clinical signs. Despite regular cervical screening, the absence of high-risk HPV infection, combined with delayed diagnosis due to atypical presentation, aggressive histology, and lack of typical gynaecologic symptoms, contributed to the poor prognosis. This clinical case highlights the need for clinicians to consider gynaecologic malignancies in women presenting with neurological symptoms, even when clinical suspicion is low. Further research is required to elucidate the molecular pathways facilitating CNS metastases and their negative prognostic implications.

INTRODUCTION

Female genital tract tumours are rare and have been classically described as "neurophobic" for their low risk of metastatization to the Central nervous system (CNS), typically associated to late stage [1]. In fact, around 1.1% of ovarian cancer, 0.59% of endometrial cancer and 0.57% of cervical cancer

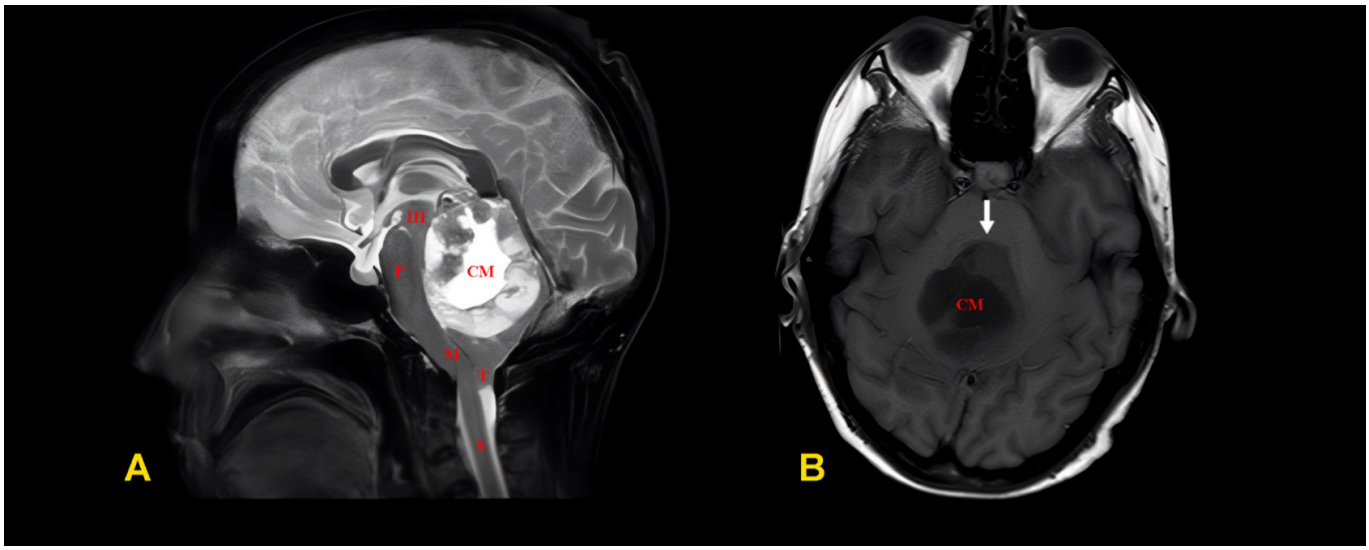

Figure 1. *Cerebral MRI.*

(A) Sagittal view**; (B)** Coronal view. The cerebellar neoformation dislocates the structures of the brainstem and obliterates the IV ventricle; CM: cerebellar mass; III: third ventricle; P: pons; M: medulla oblungata; T: herniated cerebellar tonsils; s: spinal cord. White arrow: obliterated IV ventricle.

(CC) metastasize to the CNS, in 50% of cases in solitary pattern [2, 3]. A valuable exception to these results is choriocarcinoma, a rare trophoblastic disease occurring in less than 0.1% of ovarian malignancies, characterized by an aggressive behaviour and a marked tendency to metastatization (about 10% of cases) [4]. Despite the direct extension and the lymphatic embolization are the most common metastatization patterns, hematogenous spread, more common in advanced disease and poorly differentiated or unusual histotype (adenosquamous or neuroendocrine), has a high prognostic value in terms of overall survival and recurrence rate of CC [5, 6]. The most common sites of distant one-site of CC metastases are lung (37.9%), bones (16.7%) and liver (12.5%), while brain metastases (BM) are rare, accounting for 1,6% of cases. However, BM are more commonly found in case of multiple site metastatization, with an overall percentage of 2.6%; in subgroup analysis BM resulted more frequently associated with bone (0.9%), lung and bone (0.7%) and lung and liver (0.4%) [7]. In this case report we describe the case of a pauci-syntomatic onset of adenocarcinoma, HPV associated, of the uterine cervix in a premenopausal woman with no remarkable past gynaecological or medical history and no initial evidence of pelvic or systemic disease.

CASE PRESENTATION

A 48 years old woman with not personal or familiar gynaecological and oncologic history, came to the Emergency Room of our hospital complaining progressive onset of headache, dizziness and gait disturbance in the last three weeks. At the neurological exam the patients resulted stuporous, with a lowered level of consciousness and nystagmus. The Glasgow Coma Scale score was 13. The patient was then referred to neuroradiology for a CT scan in suspected stroke. The CT scan showed sign of obstructive hydrocephalus, due to a mass in the IV ventricle. The patient moved to the neurosurgical ward where underwent an urgent drainage of the cerebro-rachidian fluid and ventriculo-peritoneal shunt. The patient was then referred to the neurosurgery unit for the stabilization of neurological conditions. A MRI was performed, showing a hypodense neoformation in the posterior cranial fossa with obliteration of the IV ventricle, anterior dislocation of the structures of the brainstem and herniation of the cerebellar tonsils with obliteration of the cerebellar-medullary liquor space. The radiological specimen is in **Figure 1**.

About one month after the hospitalization, the patient underwent a craniectomy and IV ventricle mass excision using Neuronavigation and Intraoperative Monitoring (IOM). The surgery had no major complications. The histopathological study of the surgical specimen revealed the presence of a single cerebellar metastasis with micropapillary and mucinous features and necrotic areas. The immunohistochemistry showed CK7+, TTF-1+ (focal), P16+. Pax8-, p40-, Sinaptophisin-, Chromogranin-suggestive of tumours of the genital tract, requiring a gynaecological evaluation. At the physical

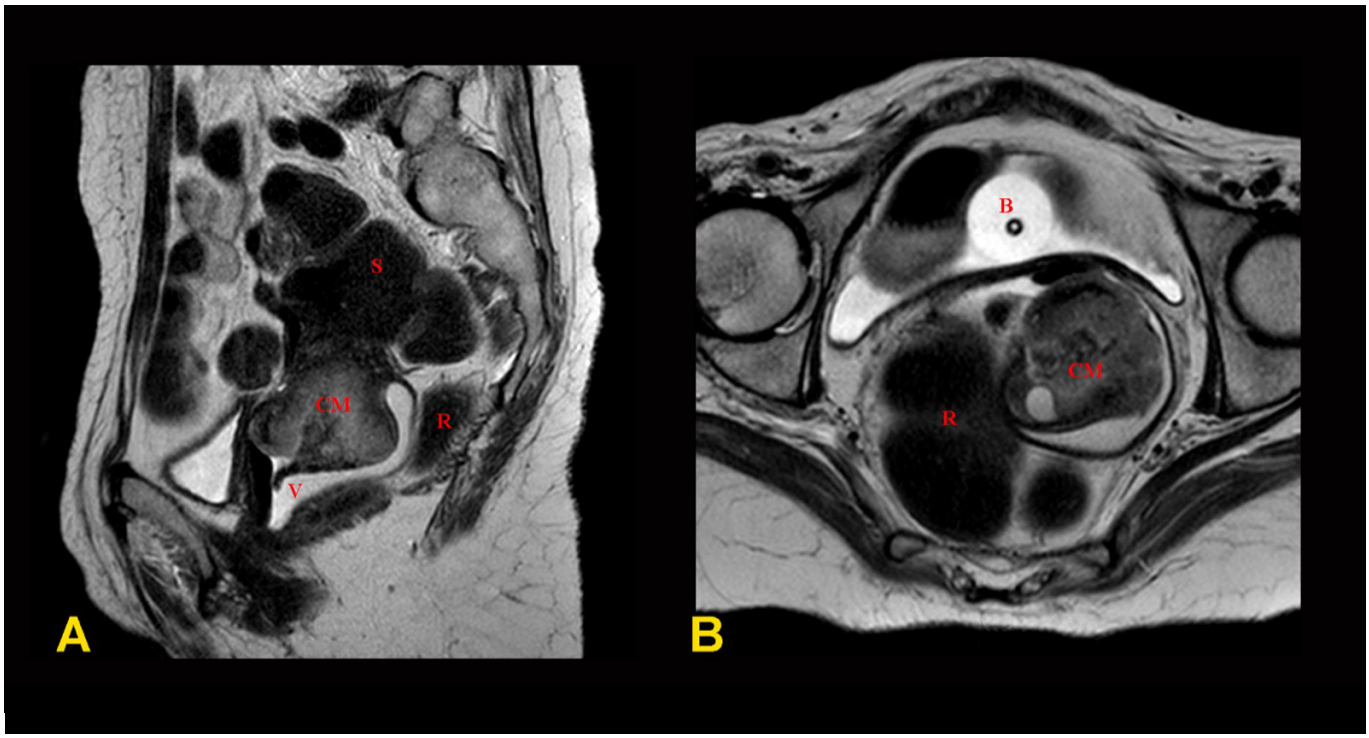

Figure 2. *Pelvic MRI.*

(A) Parasagittal left view; **(B)** Coronal view. The cervical neoformation extended for about 6 cm x 2.5 cm x 5 cm in close contiguity with the lateral wall of the rectum. There is a concomitant fluid distention of the fornix and the vaginal lumen; CM: cervical mass; R: rectum; S: sigma; V: vagina; B: bladder (evidence of Foley balloon).

examination with speculum, we noticed an irregular barrel-shaped portio with friable tissue on the anterior cervical labium, with suspect of extension into vaginal fornices. On bimanual vagino-rectal examination, the cervix was enlarged and indurated, with a firm, irregular consistency suggestive of malignant infiltration. There was bilateral parametrial involvement extending laterally toward the pelvic sidewalls, consistent with locally advanced disease. The vaginal and esocervical mucosa appeared intact, and no mucous or bloody discharge was observed during the examination. A transvaginal office ultrasound was performed, revealing a richly vascularized iso- to hyperechogenic mass located in the upper third of the uterine cervix, measuring up to 60 mm in maximum diameter. Stromal infiltration was estimated to exceed 75%, with no lateral tumor-free distance and no cranial tumor-free margin. Parametrial involvement was extensive, characterized by grade 3 to grade 4 nodular infiltration. An initial suspicion of bladder and rectal invasion was raised due to a negative sliding sign. No suspicious lymph nodes were identified. Both ureters were displaced by the tumor mass, although there was no evidence of hydroureteronephrosis. Transabdominal examination revealed no lymphadenopathy or secondary expansive lesions. A colposcopic examination confirmed an irregular, barrel-shaped cervix; however, the assessment was deemed unsatisfactory due to non-visualization of the squamocolumnar junction, consistent with a Type III transformation zone. We performed an ambulatorial hysteroscopy in order to obtain a biopsy of the cervical lesion. Then the histological assay of the cervical specimen showed neoplasia fragment within necrotic/haemorrhagic tissue. The immunohistochemical assay turned positive for CK7, TTF-1, p16 and negative for P40, Synaptophysin, Chromogranin A and PAX8. The final diagnosis was poorly differentiated adenocarcinoma of probable endocervical origin.

An abdominal/pelvic RMN was performed. The imaging, strongly suspected for cervical neoplasm, showed a heterologous expansive mass in correspondence of the superior III of the uterine cervix extended for about 6 cm × 2.5 cm × 5 cm with concomitant fluid distention of the fornix and the vaginal lumen. The mass assumed a close contiguity with the lateral wall of the rectum but without clear signs of infiltration. In consideration of the cerebellar metastasis, the neoformation was evaluated staging IVB for International Federation of Obstetrics and Gynecology. The MRI is showed in **Figure 2**.

Table 1. *Main characteristics of patients included in the study.*

First author	Year	Age at diagnoses	FIGO Stage	Grade	Histology	Treatment
Weed *et al.* [33]	1975	47	IV	G3	SCC	RT
Kumar *et al.* [34]	1994	48	III	G3	ADK	RT
Kumar *et al.* [34]	1994	50	IV	G3	SCC	RT
Lefkowitz *et al.* [8]	1983	29	I	G2	SMCC	DEB + RT
Lefkowitz *et al.* [8]	1983	31	III	G3	SCC	DEB + RT
Lefkowitz *et al.* [8]	1983	68	III	G2	ADSQ	RT
Robinson *et al.* [35]	1997	68	III	G2	SCC	CHT + RT
Cormio *et al.* [36]	1999	49	II	G3	SCC	DEB ONLY
Ziainia *et al.* [37]	1999	38	II	G3	SCC	RT
Cormio *et al.* [38]	2000	42	IV	G3	ADK	DEB + RT
Salpietro *et al.* [39]	2000	44	III	G3	SCC	RT
Tajran *et al.* [40]	2003	59	I	G3	ADK	DEB ONLY
El omari *et al.* [41]	2003	48	I	G3	SCC	DEB + RT
El omari *et al.* [41]	2003	67	II	G3	SCC	RT
Wuntkal *et al.* [42]	2004	44	IV	G3	ADK	ONLY CHT
Salvati *et al.* [43]	2005	50	III	G3	ADK	CHT + RT
Salvati *et al.* [43]	2005	48	II	G3	SCC	RT
Rentinck *et al.* [44]	2004	54	II	G2	SCC	CHT + RT
Nagar *et al.* [45]	2005	72	II	G2	ADK	DEB + CHT
Amita *et al.* [46]	2005	54	II	G3	SCC	CHT + RT
Portera *et al.* [47]	2006	43	I	G3	SCC	DEB ONLY
Gaussmann et al [48]	2006	36	I	G3	SCC	DEB ONLY
Cordeiro *et al.* [10]	2006	31	II	G1	ADK	DEB + RT
Cordeiro *et al.* [10]	2006	60	IV	G1	ADK	NO TREATMENT
Agrawal *et al.* [49]	2007	46	II	G2	SCC	DEB + RT
Balaji *et al.* [50]	2007	50	IV	G3	SCC	NO TREATMENT
Brown *et al.* [51]	2007	60	IV	G2	ADSQ	DEB ONLY
Peters P. *et al.* [52]	2010	38	II	G2	SCC	RT
Peters P. *et al.* [52]	2010	38	IV	G3	SCC	CHT + RT
Park *et al.* [53]	2010	45	I	G3	SCC	DEB + RT
Komiyama *et al.* [54]	2011	33	I	G2	NEC	DEB + CHT
Ding *et al.* [55]	2010	39	I	G3	SCC	DEB + RT
Marongiu *et al.* [56]	2012	34	IV	G3	SCC	DEB + CHT + RT
Marongiu *et al.* [56]	2012	48	IV	G2	NEC	DEB + CHT
Setoodeh *et al.* [57]	2012	53	IV	G3	ADSQ	NO TREATMENT
Setoodeh et al [57]	2012	43	IV	G2	SCC	NO TREATMENT
Setoodeh *et al.* [57]	2012	53	IV	G3	SCC	NO TREATMENT
Chekrine *et al.* [58]	2013	44	I	G3	SCC	DEB + CHT + RT
Scutiero *et al.* [59]	2013	50	II	G3	SMCC	DEB + CHT
Erdis *et al.* [60]	2014	67	IV	G2	SCC	ONLY CHT
Branch *et al.* [61]	2014	46	IV	G3	SCC	CHT + RT
Sato *et al.* [62]	2015	50	IV	G3	SCC	CHT + RT
Pyeon *et al.* [63]	2015	44	II	G3	SMCC	DEB + CHT
Gupta *et al.* [64]	2016	52	IV	G2	ADK	DEB + CHT + RT
Fetcko *et al.* [65]	2017	68	III	G3	SCC	CHT + RT
Fantini *et al.* [66]	2017	41	II	G3	SCC	DEB ONLY
Hwang *et al.* [67]	2018	45	III	G3	ADK	DEB + CHT
Chakrabarti *et al.* [68]	2019	52	II	G3	SCC	CHT + RT
Yalan *et al.* [69]	2019	49	I	G3	SCC	DEB ONLY
Yalan *et al.* [69]	2019	48	IV	G3	SCC	NO TREATMENT
Mori *et al.* [70]	2020	46	I	G3	NEC	DEB + CHT
Hernandez *et al.* [71]	2022	34	IV	G3	SCC	NO TREATMENT
Dai *et al.* [72]	2023	33	IV	G3	SCC	CHT
Kimata *et al.* [73]	2023	53	III	G3	ADSQ	NO TREATMENT

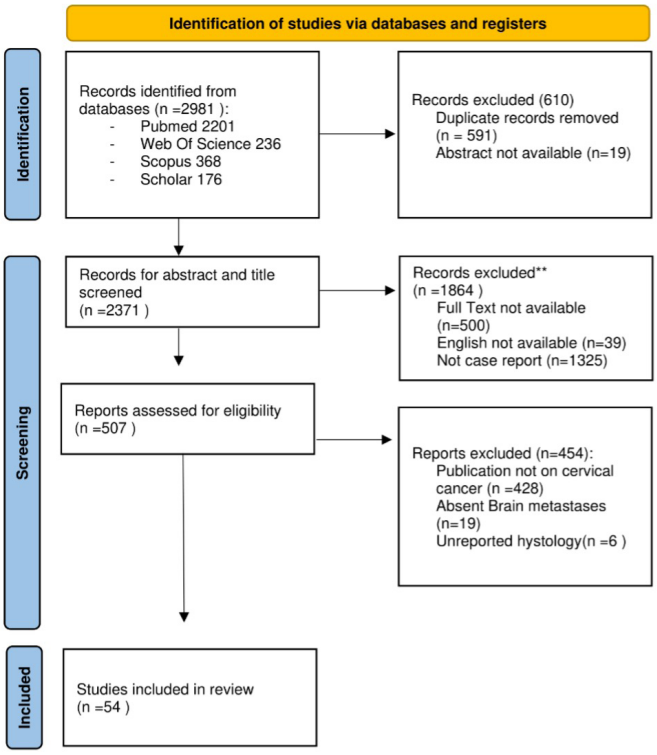

Figure 3. *PRISMA 2020 flow diagram.*

Table 2. *FIGO staging and grading stratified by histotype.*

	FIGO staging				Grading		
Histology	I	II	III	IV	G1	G2	G3
SCC	8	10	4	12	0	6	28
ADK	1	2	3	4	2	2	6
ADSQ	0	0	2	2	0	2	2
SMCC	1	2	0	0	0	1	2
NEC	2	0	0	1	0	2	1
Total	**12**	**14**	**9**	**19**	**2**	**13**	**39**

SCC: squamous cell carcinoma; ADK: cervical adenocarcinoma; ADSQ: cervical adenosquamous carcinoma; SMCC: small cell cervical carcinoma; NEC: neuroendocrine cervical carcinoma.

A full blood assessment showed an increase of CEA 182.0 ng/mL and Cyfra 21 – 1. 12.7 ng/mL CA19.9, SCC-A and NSE were negative.

The multidisciplinary team of our University Hospital, in consideration of the FIGO grade IVB and the poor performance status, esteemed the patient not eligible to chemotherapy or pelvic radiotherapy/brachytherapy and addressed her to cerebellar radiotherapy and subsequent palliative care. The patient was subjected to three cycles of cerebellar radiotherapy and after eight months of palliative care, deceased.

DISCUSSION

We used the PRISMA 2020 methodology for the selection of pertinent articles as outlined in **Figure 3**. We used IBM® SPSS® to calculate the statistics. A total of 54 case reports were included in our review (no automation was used to select cases) The statistical tools that we used were t-test and ANOVA to compare means and chi squared test to examine categorical variables. Kaplan-Meyer curves were used for survival analysis.

We enlisted 54 cases of cervical cancer with CNS metastases as reported in **Table 1.** The mean age at diagnosis was 48.0 ± 10. The youngest woman was 29 [8], and the oldest was 72 [9]. The mean age at diagnoses was stratified by hystology type, with a mean age at diagnoses significantly augmented for adenosquamous carcinoma (58.5 ± 7.14, $p < 0.049$) and a mean age at diagnoses significantly reduced for rare hystotype of small cell carcinoma (41.6 ± 9.7 $p < 0.049$) and neuroendocrine cell carcinoma (37.6 ± 7.2 $p < 0.049$). Mean age of squamous cell carcinoma (47.6) and squamous adenocarcinoma (50.1) were in the mean.

The FIGO staging, and definitive hystology were reported in 100% of included cases. The most common staging at diagnoses was FIGO IV (35%, n = 19) and FIGO II (26%, n = 14). Almost 72% of cancers were poorly differentiated G3 (n = 39). We enlisted only 2 cases of good differentiated G1 (3.7%) [10]. The hystopathology was in 63% of cases squamous cell carcinoma (n = 34), 18.5 of cases adenocarcinoma (n = 10), 7.4% of cases adenosquamous carcinoma (n = 4). Rare hystotype were small cell carcinoma 5.6% (n = 3) and neuroendocrine carcinoma 5.6% (n = 3). Extensive results are expressed in **Table 2**.

The mediana of survival of patients from the diagnoses was 13 weeks. Comparing the hystotype there were a statistical significative difference in survival (Log-rank Mantel-Cox 7.77, $p < 0.049$), especially for small cell carcinoma (medium survival 7 weeks from diagnoses) and neuroendocrine carcinoma (medium survival 13 weeks from the diagnoses).

Only in a small portion of patients (15%) the metastases were diagnosed together with the cervical cancer, while the mean time of occurrence of the metastases from the diagnosis of cervical neoplasia was at 36 months (70% of cases). In the 64% of cases there were isolated metastases. The most common locations of brain metastases were brain

Table 3. *Treatment of choice for cervical cancer.*

Treatment		n°	%
Primary debulking	Plus radio	9	16.7
	Plus chemio	7	13.0
	With no therapy	7	13.0
	Plus concomitant chemoradiotherapy	3	5.6
Primary	Radiotherapy	9	16.7
	Chemoradiotherapy	9	16.7
	Chemiotherapy	2	3.7
No treatment		8	14.8
Total		**54**	**100.0**

(55.6%) and meningeal (14.8%). Cerebellar metastases were rare (14.8%). In only 5 cases (9.3%) there was the contemporary involvement of brain and cerebellum. The clinical presentation of CNS metastases was symptomatic in 48% of cases, with predominance of symptoms of headache (51.9%), vision impairment (24.1%) and vertigo/ataxia/postural instability (24,1%). Less frequent symptoms were seizures (16.7%) and plegia (13%). The 48% of patients was subjected to primary debulking (n = 26), with subsequent radiotherapy in 16.7% of cases (n = 9), chemotherapy in 13.0% (n = 7) and no therapy in 13% (n = 7). 51% of the patients were not subjected to primary debulking (n = 28) and was subjected to primary radiotherapy in 16.7% of cases (n = 9) and primary chemoradiotherapy in 16.7% of cases (n = 9). The results are in **Table 3**. In 14.8% of cases the patient underwent palliative care only (n = 8). As expected, the choice of treatment resulted no significatively related to grading ($p = 0.83$) or histology ($p = 0.14$) but to FIGO staging (Chi Square 35.4, Cramer V: 0.46, $p < 0.008$). The CNS metastases was resected in 54% of cases (n = 29), followed in 64% of cases (n = 18) by adjuvant radiotherapy. In 32% of cases (n = 17) a primary radiotherapy was performed. In 13% of cases (n = 7) cases the patient was addressed to palliative care.

Worldwide, CC is the fourth most common neoplasia affecting women and the most common tumour of the women genital tract for numbers of new cases (604.127) and new deaths (341.813) in 2020 [11-17]. The main cause of cervical cancer is persistent sexually transmitted infection by Human Papillomavirus (HPV). There are over 200 strains of HPV, but CC is related to oncogenic ones, such as HPV-16, HPV-33, HPV-18, HPV-31, HPV-45, HPV-52, HPV-58 [18], in particular HPV16 and HPV18 account for 50% and 15% of CC [16, 17]. Currently several prevention modalities are available for cervical carcinoma [19]. First, the use of barrier contraception methods is essential to avoid HPV infection. Moreover, available scientific evidence indicates that HPV vaccination, recommended during adolescence for both sexes, can limit the incidence of infection and reduce the occurrence of precancerous lesions and of CC by 85% in vaccinated women [20]. In addition, screening modalities, such as cervical cytology (Pap test), primary screening with HPV test, and co-testing with HPV and cytology, allow the early identification of cervical lesions. In Low- and Middle-Income Countries (LMIC) countries, where screening programs are lacking, the incidence of cervical cancer is higher, accounting for 84% of CC cases and 87% of CC deaths [12, 13].

Finally, tertiary prevention focuses on the treatment of previously identified lesions. LEEP (Loop Electrosurgical Excision Procedure) is a safe, widepread and effective surgical procedure capable to diagnose, treat and prognose non-invasive lesions of the cervix [21]. In CC, the therapeutic approach varies depending on the stage at diagnosis. The 2023 European Society of Gynaecological Oncology (ESGO) guidelines, with the European Society for Radiotherapy and Oncology (ESTRO) and the European Society of Pathology (ESP), supported the minimally invasive surgery as a potential option for low-risk tumours (diameter of less than 2 cm and negative margins after conization), but the LACC (Laparoscopic Approach to Carcinoma of the Cervix) study raised questions about the outcomes, showing a four-fold higher recurrence rate and a six-fold higher all-cause mortality rate compared to laparotomy [22].

Moreover, HPV persistence, as well as viral load, are considered two of the main risk factors impacting the risk of cervical dysplasia recurrence. The risk of CIN2+ recurrence increased with the increase of HPV persistence for up to 1 year [23]. Other main risk factors influencing the risk of cervical dysplasia recurrence include patients' age, positive margin status, and severity of the lesions [24]. According to preliminary research, it seems that HPV vaccination can also be adopted in order to reduce the risk of dysplasia of the lower genital tract in women previously hysterectomized for high gra-

de cervical intraepithelial neoplasia (CIN2+) and early-stage cervical cancer [25].
The most widely used staging system for cervical cancer is the International Federation of Gynecology and Obstetrics (FIGO) staging system [26].
In the Piura and Piura's literature review, only 96 cases were reported, with an incidence of 0.57%. The brain metastasis was part of a disseminated recurrence in 53.2% of patients, was solitary in 50.6%, and was located only in the cerebrum in 73% of patients [1]. According to a study of Hwang *et al.*, the median age of patients with brain metastases from cervical cancer at the diagnosis is 50 years; among the 11 patients involved in this study, five (45.5%) of them had squamous cell carcinoma, three had adenocarcinoma, two had small cell carcinoma and one had adenosquamous cell carcinoma [27]. Brain metastases usually develop lately in the clinical history of the patients (median interval between diagnosis of cervical carcinoma and evidence of CNS metastases of 18 months), but in some uncommon cases isolated brain metastasis can be the initial site of presentation of this neoplasia, with no other gynaecologic symptoms or systemic metastases [28, 29]. Brain metastasis from cervical carcinoma is usually incurable, and the median survival from the diagnosis to the death is 2.3 months. Factors apparently associated to a better prognosis are age ≤ 50 years, good performance status, single brain metastasis, no evidence of extracranial metastases [30]. Most of the CNS metastases from cervical cancer are in the supratentorial region, maybe according to its vascular and spatial characteristics, and are diagnosed with CT or MRI scans that allow to restage the neoplasia too. Neurological symptoms are usually present. Headache is the most common symptom reported in many studies, but, depending on the CNS region involved by the metastatic process, it is possible to observe other signs and symptoms, like confusion, paralysis, seizures, nausea and vomiting due to increased intracranial pressure, vertigo, amnesia, gait disturbances; these signs and symptoms could be present alone or combined [31]. Brain metastases are the most common brain tumours in adults, but the molecular and biological mechanisms that facilitate the formation of CNS metastases are still poorly understood. It is known that the organotropism of tumour cells depends on various factors, such as circulatory and anatomical proximity, metastatic niche, and tumour cell intrinsic factors, and that the interactions between the tumour cell intrinsic factors and the metastatic brain niche microenvironment is known as the "seed and soil" hypothesis [32].

CONCLUSIONS

Our case can be interesting cause of the silent trend of the cervical neoplasia in this woman, that went to the Emergency Room cause of symptoms related to apparently unlinked organs (brain, cerebellum). Extra pelvic signs and symptoms were the only clue to this neoplasia, the metastasis gave sign of its presence with a severe intracranial hypertension in a woman with apparently no remarkable gynaecologic history. In this case, cervical cancer progressed silently and disseminated to the brain without prior involvement of other organs. This is atypical, as metastatic cervical cancer is more commonly associated with widespread disease at the time of diagnosis, most frequently involving the lungs, with brain metastases typically occurring at later stages. Moreover, the oncomarker that is more often associated to cervical malignancies, that is SCC – A (Squamous Cell Carcinoma – Antigen), was negative. This case can be a cue to investigate further with an accurate gynaecological assessment and with total body imaging when CNS tumours are detected, and to focus on a possible cervical/gynaecological cancer as a primary neoplasia even when the oncomarkers mainly linked to gynaecological malignancies are negative, avoiding to use oncomarkers in order to make diagnosis; in fact, cervical adenocarcinoma is less common than the squamous cell carcinoma, for this reason even when SCC – A is negative the diagnosis of a cervical neoplasia cannot be excluded. This case could be a proof that oncomarkers reliability can be only optimal for the follow up of patients with a previously established oncological diagnosis. Furthermore, no information was available regarding recent cervical cancer screening for the patient described in this case. This absence may reflect a broader issue: women who do not regularly participate in screening programs may be at greater risk of developing malignancies that progress silently and remain undetected until reaching an advanced or terminal stage. This case underscores the critical importance of regular cervical cancer screening - such as the Pap smear and HPV testing - and serves as a reminder for clinicians to actively promote adherence to established screening protocols among eligible populations.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contributions

M.C.: Data curation, formal analysis, visualization, writing – original draft, writing – review & editing. M.Ba, A.A.: Data curation, writing – original draft, writing – review & editing. M.M., M.Be: Data curation, writing – original draft. A.G.: Visualization, writing – review & editing. M.D. A.V.: Investigation, methodology, data curation. G.C., E.C: Supervision, conceptualization, project administration. M.M.: Supervision, conceptualization, project administration, writing – review & editing.

Funding

None.

Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

Ethics Committee approval was not necessary since the study was a summary of data and outcomes of routine management (without direct intervention) and not an experimental protocol. We ensured the complete anonimacy of the patients.

Informed consent

Written informed consent was obtained from the patient to publish this paper.

Data sharing

All data are reported in the text and tables.

REFERENCES

1. Piura E, Piura B. Brain metastases from endometrial carcinoma. ISRN Oncol. 2012;2012:581749. doi: 10.5402/2012/581749.
2. Zhang Y, Grant MS, Stepp WH, Clark LH. Clinical characteristics of CNS metastases from primary gynecologic cancers. Gynecol Oncol Rep. 2019;30:100518. doi: 10.1016/j.gore.2019.100518.
3. Hacker NF, Rao A. Surgical management of lung, liver and brain metastases from gynecological cancers: a literature review. Gynecol Oncol Res Pract. 2016;3:7. doi: 10.1186/s40661-016-0028-3.
4. Athanassiou A, Begent RH, Newlands ES, Parker D, Rustin GJ, Bagshawe KD. Central nervous system metastases of choriocarcinoma. 23 years' experience at Charing Cross Hospital. Cancer. 1983;52(9):1728-35. doi: 10.1002/1097-0142(19831101)52:9<1728::aid-cncr2820520929>3.0.co;2-u.
5. Patterson MR, Cogan JA, Cassidy R, Theobald DA, Wang M, Scarth JA, et al. The Hippo pathway transcription factors YAP and TAZ play HPV-type dependent roles in cervical cancer. Nat Commun. 2024;15(1):5809. doi: 10.1038/s41467-024-49965-9.
6. Shan Y, Ding Z, Cui Z, Chen A. Incidence, prognostic factors and a nomogram of cervical cancer with distant organ metastasis: a SEER-based study. J Obstet Gynaecol. 2023;43(1):2181690. doi: 10.1080/01443615.2023.2181690.
7. Zhou S, Peng F. Patterns of metastases in cervical cancer: a population-based study. Int J Clin Exp Pathol. 2020;13(7):1615-23.
8. Lefkowitz D, Asconapé J, Biller J. Intracranial metastases from carcinoma of the cervix. South Med J. 1983;76(4):519-21. doi: 10.1097/00007611-198304000-00032.
9. Nagar YS, Shah N, Rawat S, Kataria T. Intracranial metastases from adenocarcinoma of cervix: a case report. Int J Gynecol Cancer. 2005;15(3):561-3. doi: 10.1111/j.1525-1438.2005.15326.x.
10. Cordeiro JG, Prevedello DM, da Silva Ditzel LF, Pereira CU, Araújo JC. Cerebral metastasis of cervical uterine cancer: report of three cases. Arq Neuropsiquiatr. 2006;64(2A):300-2. doi: 10.1590/s0004-282x2006000200023.
11. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249. doi: 10.3322/caac.21660.
12. Li K, Xu H, Wang S, Qin P, Liang B. Disparities in the increases of cervical cancer incidence rates: observations from a city-wide population-based study. BMC Cancer. 2022;22(1):419. doi: 10.1186/s12885-022-09531-2.
13. Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. Lancet. 2019;393(10167):169-82. doi: 10.1016/S0140-6736(18)32470-X.
14. Wolf J, Kist LF, Pereira SB, Quessada MA, Petek H, Pille A, et al. Human papillomavirus infection: Epidemiology, biology, host interactions, cancer development, prevention, and

therapeutics. Rev Med Virol. 2024;34(3):e2537. doi: 10.1002/rmv.2537.
15. Huang F, He L, Li W, Huang X, Zhang T, Muaibati M, et al. HPV integration: a precise biomarker for detection of residual/recurrent disease after treatment of CIN2-3. Infect Agent Cancer. 2024;19(1):36. doi: 10.1186/s13027-024-00600-8.
16. Clifford G, Franceschi S. Members of the human papillomavirus type 18 family (alpha-7 species) share a common association with adenocarcinoma of the cervix. Int J Cancer. 2008;122(7):1684-5. doi: 10.1002/ijc.23282.
17. Smith JS, Lindsay L, Hoots B, Keys J, Franceschi S, Winer R, et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. Int J Cancer. 2007;121(3):621-32. doi: 10.1002/ijc.22527.
18. Jaisamrarn U, Castellsagué X, Garland SM, Naud P, Palmroth J, Del Rosario-Raymundo MR, et al. Natural history of progression of HPV infection to cervical lesion or clearance: analysis of the control arm of the large, randomised PATRICIA study. PLoS One. 2013 19;8(11):e79260. doi: 10.1371/journal.pone.0079260. Erratum in: PLoS One. 2013;8(12). doi:10.1371/annotation/cea59317-929c-464a-b3f7-e095248f229a.
19. Ferrari F, Giannini A. Approaches to prevention of gynecological malignancies. BMC Womens Health. 2024;24(1):254. doi: 10.1186/s12905-024-03100-4.
20. Hariri S, Unger ER, Schafer S, Niccolai LM, Park IU, Bloch KC, et al. HPV type attribution in high-grade cervical lesions: assessing the potential benefits of vaccines in a population-based evaluation in the United States. Cancer Epidemiol Biomarkers Prev. 2015;24(2):393-9. doi: 10.1158/1055-9965.EPI-14-0649.
21. Golia D'Augè T, Cuccu I, Etrusco A, D'Amato A, Lagana AS, D'Oria O, et al. State of the art on HPV-related cervical lesions. 2024;36(2)135-7. doi: 10.36129/jog.2024.161.
22. Cibula D, Raspollini MR, Planchamp F, Centeno C, Chargari C, Felix A, et al. ESGO/ESTRO/ESP Guidelines for the management of patients with cervical cancer - Update 2023. Int J Gynecol Cancer. 2023;33(5):649-66. doi: 10.1136/ijgc-2023-004429.
23. Bogani G, Sopracordevole F, Ciavattini A, Vizza E, Vercellini P, Giannini A, et al. Duration of human papillomavirus persistence and its relationship with recurrent cervical dysplasia. Eur J Cancer Prev. 2023;32(6):525-32. doi: 10.1097/CEJ.0000000000000822.
24. Bogani G, Tagliabue E, Ferla S, Martinelli F, Ditto A, Chiappa V, et al. Nomogram-based prediction of cervical dysplasia persistence/recurrence. Eur J Cancer Prev. 2019;28(5):435-40. doi: 10.1097/CEJ.0000000000000475.
25. Bogani G, Sopracordevole F, Ciavattini A, Ghelardi A, Vizza E, Vercellini P, et al. HPV-related lesions after hysterectomy for high-grade cervical intraepithelial neoplasia and early-stage cervical cancer: A focus on the potential role of vaccination. Tumori. 2024;110(2):139-45. doi: 10.1177/03008916231208344.
26. Int J Gynaecol Obstet. 2019;145(1):129-35. doi: 10.1002/ijgo.12749. Erratum in: Int J Gynaecol Obstet. 2019;147(2):279-80. doi: 10.1002/ijgo.12969.
27. Hwang DW, Song HS, Choi YY, Kim HS, Kim YA, Chun KC. Primary non-gestational choriocarcinoma of the uterine cervix with metaplastic transformation from adenocarcinoma: a case report. J Obstet Gynaecol. 2018;38(2):289-90. doi: 10.1080/01443615.2017.1336756.
28. Sato Y, Tanaka K, Kobayashi Y, Shibuya H, Nishigaya Y, Momomura M, et al. Uterine cervical cancer with brain metastasis as the initial site of presentation. J Obstet Gynaecol Res. 2015;41(7):1145-8. doi: 10.1111/jog.12668.
29. Cormio G, Pellegrino A, Landoni F, Regallo M, Zanetta G, Colombo A, et al. Brain metastases from cervical carcinoma. Tumori. 1996;82(4):394-6. doi: 10.1177/030089169608200420.
30. Li H, Wu X, Cheng X. Advances in diagnosis and treatment of metastatic cervical cancer. J Gynecol Oncol. 2016;27(4):e43. doi: 10.3802/jgo.2016.27.e43.
31. Chura JC, Shukla K, Argenta PA. Brain metastasis from cervical carcinoma. Int J Gynecol Cancer. 2007;17(1):141-6. doi: 10.1111/j.1525-1438.2007.00808.x.
32. Campbell BK, Gao Z, Corcoran NM, Stylli SS, Hovens CM. Molecular Mechanisms Driving the Formation of Brain Metastases. Cancers (Basel). 2022;14(19):4963. doi: 10.3390/cancers14194963.
33. Weed JC Jr, Creasman WT. Meningeal carcinomatosis secondary to advanced squamous cell carcinoma of the cervix: a case report. Meningeal metastasis of advenced cervical cancer. Gynecol Oncol. 1975;3(3):201-4. doi: 10.1016/s0090-8258(75)80003-5.

34. Kumar L, Kaushal R, Nandy M, Biswal BM, Kumar S, Kriplani A, et al. Chemotherapy followed by radiotherapy versus radiotherapy alone in locally advanced cervical cancer: a randomized study. Gynecol Oncol. 1994;54(3):307-15. doi: 10.1006/gyno.1994.1215.
35. Robinson JB, Morris M. Cervical carcinoma metastatic to the brain. Gynecol Oncol. 1997;66(2):324-6. doi: 10.1006/gyno.1997.4763.
36. Cormio G, Colamaria A, Loverro G, Pierangeli E, Di Vagno G, De Tommasi A, et al. Surgical resection of a cerebral metastasis from cervical cancer: case report and review of the literature. Tumori. 1999;85(1):65-7. doi: 10.1177/030089169908500114.
37. Ziainia T, Resnik E. Hemiballismus and brain metastases from squamous cell carcinoma of the cervix. Gynecol Oncol. 1999;75(2):289-92. doi: 10.1006/gyno.1999.5551.
38. Cormio G, Colamaria A, Di Vagno G, De Tommasi A, Loverro G, Selvaggi L. Surgical decompression and radiation therapy in epidural metastasis from cervical cancer. Eur J Obstet Gynecol Reprod Biol. 2000;89(1):59-61. doi: 10.1016/s0301-2115(99)00165-7.
39. Salpietro FM, Romano A, Alafaci C, Tomasello F. Pituitary metastasis from uterine cervical carcinoma: a case presenting as diabetes insipidus. Br J Neurosurg. 2000;14(2):156-9. doi: 10.1080/02688690050004651.
40. Tajran D, Berek JS. Surgical resection of solitary brain metastasis from cervical cancer. Int J Gynecol Cancer. 2003;13(3):368-70. doi: 10.1046/j.1525-1438.2003.13189.x.
41. Omari-Alaoui HE, Gaye PM, Kebdani T, El Ghazi E, Benjaafar N, Mansouri A, et al. Cerebellous metastases in patients with uterine cervical cancer. Two cases reports and review of the literature. Cancer Radiother. 2003;7(5):317-20. doi: 10.1016/s1278-3218(03)00085-4.
42. Wuntkal R, Maheshwari A, Kerkar RA, Kane SV, Tongaonkar HB. Carcinoma of uterine cervix primarily presenting as carcinomatous meningitis: a case report. Aust N Z J Obstet Gynaecol. 2004;44(3):268-9. doi: 10.1111/j.1479-828X.2004.00209.x.
43. Salvati M, Caroli E, Paone C, Frati A, Ferrante L, Giangaspero F, et al. Brain metastasis from cutaneous squamous cell carcinoma of the dorsum. Case report. J Neurosurg. 2005;102(6):1155-8. doi: 10.3171/jns.2005.102.6.1155.
44. Rentinck ME, Schrijver HM, Kneppers E, Zijlmans JC, van Groeningen CJ. Carcinomatous meningitis in cancer of the uterine cervix. J Neurooncol. 2004;70(1):87-90. doi: 10.1023/b:neon.0000040836.20884.fc.
45. Nagar YS, Shah N, Rawat S, Kataria T. Intracranial metastases from adenocarcinoma of cervix: a case report. Int J Gynecol Cancer. 2005;15(3):561-3. doi: 10.1111/j.1525-1438.2005.15326.x.
46. Amita M, Sudeep G, Rekha W, Yogesh K, Hemant T. Brain metastasis from cervical carcinoma--a case report. MedGenMed. 2005;7(1):26.
47. Portera CC, Gottesman RF, Srodon M, Asrari F, Dillon M, Armstrong DK. Optic neuropathy from metastatic squamous cell carcinoma of the cervix: an unusual CNS presentation. Gynecol Oncol. 2006;102(1):121-3. doi: 10.1016/j.ygyno.2006.01.040.
48. Gaussmann AB, Imhoff D, Lambrecht E, Menzel C, Mose S. Spontaneous remission of metastases of cancer of the uterine cervix. Onkologie. 2006;29(4):159-61. doi: 10.1159/000091645.
49. Agrawal A, Kumar A, Sinha AK, Kumar M, Pandey SR, Khaniya S. Intracranial metastases from carcinoma of the cervix. Singapore Med J. 2007;48(5):e154-6.
50. Balaji R, Ramachandran K, Kumar A, Krishnakumar AS, Venugopal M. Pachymeningeal metastasis from squamous cell carcinoma of the uterine cervix with involvement of the optic nerve: case report and review of the literature. Cancer Imaging. 2007;7(1):138-40. doi: 10.1102/1470-7330.2007.0020.
51. Brown Iii JV, Epstein HD, Kim R, Micha JP, Rettenmaier MA, et al. Rapid manifestation of CNS metastatic disease in a cervical carcinoma patient: a case report. Oncology. 2007;73(3-4):273-6. doi: 10.1159/000127426.
52. Peters P, Bandi H, Efendy J, Perez-Smith A, Olson S. Rapid growth of cervical cancer metastasis in the brain. J Clin Neurosci. 2010;17(9):1211-2. doi: 10.1016/j.jocn.2010.01.021.
53. Park SH, Ro DY, Park BJ, Kim YW, Kim TE, Jung JK, et al. Brain metastasis from uterine cervical cancer. J Obstet Gynaecol Res. 2010;36(3):701-4. doi: 10.1111/j.1447-0756.2010.01219.x.
54. Komiyama S, Nishio E, Torii Y, Kawamura K, Oe S, Kato R, et al. A case of primary uterine cervical neuroendocrine tumor with meningeal carcinomatosis confirmed by diagnostic imaging and

autopsy. Int J Clin Oncol. 2011;16(5):581-6. doi: 10.1007/s10147-010-0155-5.
55. Ding DC, Chu TY. Brain and intramedullary spinal cord metastasis from squamous cell cervical carcinoma. Taiwan J Obstet Gynecol. 2010;49(4):525-7. doi: 10.1016/S1028-4559(10)60111-8.
56. Marongiu A, Salvati M, D'Elia A, Arcella A, Giangaspero F, Esposito V. Single brain metastases from cervical carcinoma: report of two cases and critical review of the literature. Neurol Sci. 2012;33(4):937-40. doi: 10.1007/s10072-011-0861-4.
57. Setoodeh R, Hakam A, Shan Y. Cerebral metastasis of cervical cancer, report of two cases and review of the literature. Int J Clin Exp Pathol. 2012;5(7):710-4.
58. Chekrine T, Hassouni A , Jouhadi H , Sahraoui S , Bouchbika Z , Taleb A., et al. [Brain metastasis of carcinoma of the cervix], Pan Afr Med J. 2013;14:114. doi: 10.11604/pamj.2013.14.114.2215.
59. Scutiero G, Loizzi V, Macarini L, Landriscina M, Greco P. Small cell carcinoma of the uterine cervix metastasising to the cerebellum. J Obstet Gynaecol. 2013;33(6):639-41. doi: 10.3109/01443615.2013.798631.
60. Erdis E. A rare metastatic region of cervix cancer; the brain. J Pak Med Assoc. 2014;64(1):89-90.
61. Branch BC, Henry J, Vecil GG. Brain metastases from cervical cancer--a short review. Tumori. 2014;100(5):e171-9. doi: 10.1700/1660.18186.
62. Sato Y, Tanaka K, Kobayashi Y, Shibuya H, Nishigaya Y, Momomura M, et al. Uterine cervical cancer with brain metastasis as the initial site of presentation. J Obstet Gynaecol Res. 2015;41(7):1145-8. doi: 10.1111/jog.12668.
63. Pyeon SY, Park JY, Ulak R, Seol HJ, Lee JM. Isolated brain metastasis from uterine cervical cancer: a case report and review of literature. Eur J Gynaecol Oncol. 2015;36(5):602-4.
64. Gupta N, Nehra P, Chauhan AS, Mehra N, Singh A, Krishnamurthy MN, et al. Cost Effectiveness of Bevacizumab Plus Chemotherapy for the Treatment of Advanced and Metastatic Cervical Cancer in India-A Model-Based Economic Analysis. JCO Glob Oncol. 2022;8:e2100355. doi: 10.1200/GO.21.00355.
65. Fetcko K, Gondim DD, Bonnin JM, Dey M. Cervical cancer metastasis to the brain: A case report and review of literature. Surg Neurol Int. 2017;8:181. doi: 10.4103/sni.sni_111_17.
66. Fantini J, Sartori A, Manganotti P. Avoiding misdiagnosis: cystic calcified brain metastases of uterine cervical cancer mimicking neurocysticercosis. BMJ Case Rep. 2017;2017:bcr2016217952. doi: 10.1136/bcr-2016-217952.
67. Hwang DW, Song HS, Choi YY, Kim HS, Kim YA, Chun KC. Primary non-gestational choriocarcinoma of the uterine cervix with metaplastic transformation from adenocarcinoma: a case report. J Obstet Gynaecol. 2018;38(2):289-90. doi: 10.1080/01443615.2017.1336756.
68. Chakrabarti D, Resu AV, Pandey A, Gupta R. Carcinoma cervix with cerebellar metastases presenting with pulmonary aspiration: a rare presentation and a rare metastatic site in a common cancer. BMJ Case Rep. 2019;12(7):e229063. doi: 10.1136/bcr-2018-229063.
69. Bi Y, Li L. Pathologically confirmed brain metastases from primary uterine cervical tumors: two cases and a literature review. World J Surg Oncol. 2019;17(1):174. doi: 10.1186/s12957-019-1720-7.
70. Mori Y, Kida Y, Matsushita Y, Mizumatsu S, Hatano M, Morita N, Tsuzuki T. Neuroendocrine Carcinoma of Uterine Cervix: Stereotactic Radiotherapy for Brain Metastasis and Stereotactic Body Radiotherapy for Renal and Pancreatic Metastases. Cureus. 2020;12(6):e8869. doi: 10.7759/cureus.8869.
71. Hernandez C, Glidden A, Sandhu M, Agrawal K, Caicedo Murillo M, Heritage C, et al. A Rare Case of Aggressive Atypical Cervical Cancer With Multi-Organ Involvement. Cureus. 2022;14(12):e32968. doi: 10.7759/cureus.32968.
72. Dai Y, Zhang Y, Ke X, Liu Y, Zang C. Cutaneous metastasis from cervical cancer to the scalp and trunk: a case report and review of the literature. J Med Case Rep. 2023;17(1):435. doi: 10.1186/s13256-023-04171-x.
73. Kimata A, Abdulrazeq H, Kritselis M, Riccelli T, Anderson M, Dowd R, et al. Metastatic cervical carcinoma to the brain masquerading as a butterfly glioma: A case report. Surg Neurol Int. 2023;14:275. doi: 10.25259/SNI_329_2023.