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Intramuscular metastatic squamous cell carcinoma of the cervix: autopsy case report

Cristiane Rúbia Ferreira[a], Leonardo de Abreu Testagrossa[b], Fernando Peixoto Ferraz de Campos[c], Marcia Yoshie Kanegae[c], Noely Paula Cristina Lorenzi[d], Ricardo Santos Simões[d]

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ABSTRACT

Cancer of the uterine cervix is the fourth leading cause of death in women in Brazil, accounting for 4800 fatal cases per year. The histology of this neoplasia is mainly represented by squamous cell carcinoma (80-85%), adenocarcinomas (10-15%), and, more rarely, mixed carcinomas. The Papanicolaou (Pap) smear test is the method of excellence in detecting incipient or pre-malignant lesions. Since its implementation, the Pap test has been reducing the incidence of this neoplasia worldwide, despite its lack of high sensitivity and specificity. Both incidence and mortality from cervical cancer have sharply decreased following the introduction of well-run screening programs. The cervical cancer typically spreads to adjacent structures by contiguity; pelvic and para-aortic lymph nodes are involved by lymphatic dissemination. Less frequently, hematogenic spread is observed, and when it occurs, the brain, breast, and skeletal muscle are rarely involved. The authors report a case of a young woman who underwent periodical gynecological examination with negative Pap tests and presented to the hospital with an advanced cervical metastatic disease involving thyroid, muscles, lymph nodes, and breast (among others sites). The diagnosis of the primary site was not elucidated during life. The patient died, and at autopsy an endophytic squamous cell carcinoma of the cervix was diagnosed.

Keywords: Neoplasms, squamous cell; Cervix uteri; Neoplasm metastasis; Muscle, skeletal.

CASE REPORT

A 33-year-old female patient, previously diagnosed with hypertension, sought medical attention complaining of a three-month history of weight loss, fever, and the emergence of axillary and supraclavicular nodules. More recently she complained of trismus and dysphagia and the emergence of similar nodules in the topography of the left thigh and right breast. She referred bloody

[a] Anatomic Pathology Service – Hospital Universitário – Universidade de São Paulo, São Paulo/SP – Brazil.
[b] Department of Pathology – Hospital das Clínicas – Faculdade de Medicina – Universidade de São Paulo, São Paulo/SP – Brazil.
[c] Department of Internal Medicine – Hospital Universitário – Universidade de São Paulo, São Paulo/SP – Brazil.
[d] Department of Gynecology – Hospital Universitário – Universidade de São Paulo, São Paulo/SP – Brazil.

vaginal discharge outside her periods, two months ago. She was using captopril and denied a family history of cancer.

Her menarche was at age 12 and first sexual intercourse at 14. She had been pregnant six times with five normal deliveries and one spontaneous abortion. The first pregnancy was at the age of 18. Her clinical and gynecological follow-up was regular. She had an active sex life and underwent tubal sterilization. Her last Pap smear was collected 2 years ago and resulted in class II. On clinical examination she was pale and emaciated. Pulmonary examination was consistent with pleural effusion in the left hemithorax. Cardiac and abdominal examinations were unremarkable. The gynecological examination revealed normal appearance of the uterine cervix on speculum examination; the external orifice was 0.5 cm opened and the bimanual touch revealed an increased uterine volume, non-movable and hardened. Breast examination revealed the presence of a 3 cm, painless nodule in the superior medial quadrant of the right breast. Several movable nodules (3 cm in its longest axis) in lymph node topography of the right supraclavicular, left axillary regions, as well as in the left thigh, were palpable.

Ultrasonography showed nodules of 2.5 cm in the vastus lateralis muscle and in the left thigh. The same lesions were evidenced in the right and left suprascapular region. A left axillary lymph node of 2.9 cm with thick liquid in its core was present. The ultrasonography also showed, in the right breast, a 2 cm nodule also exhibiting central necrosis. Transvaginal ultrasonography was considered normal. Cervical lymph node biopsy revealed a poorly differentiated metastatic carcinoma with necrosis and extra capsular extension into the adjacent adipose tissue. Immunohistochemistry is presented in Table 1.

Table 1 – Immunohistochemical panel used in the lymph node biopsy

Antigen	Result	Antigen	Result
ER	Negative	Citoqueratine 7	Positive
PR	Negative	Citoqueratine 20	Negative
TTF1	Negative	CEA	Positive rare cells
Tg	Negative	34BE12	Positive
BRST 2	Negative	35BH11	Positive weak

BRST = breast; CEA = carcinoembryonic antigen; ER = estrogen receptor; PR = progesterone receptor; Tg = thyroglobulin; TTF1 = thyroid transcription factor.

The immunohistochemical analysis associated with the morphologic findings allowed the diagnosis of poorly differentiated adenocarcinoma with ductal and squamous differentiation, disadvantaging the primary site of origin as breast, colon, lung, stomach, and thyroid (Figure 1). The correlation between immunohistochemical, clinical, and histological results favored the possibility of the salivary glands being the primary tumor.

The patient underwent head, neck, and chest computed tomography (CT), which ruled out the involvement of the parotid, submandibular, and sublingual glands. This examination also showed a heterogeneous enhancement of the contrast in the right and left supraclavicular fossa, skin, and subcutaneous tissues of the breast and left thoracic and abdominal wall. The brain CT scan showed diffuse hypoatenuating areas.

The patient's outcome was unfavorable with respiratory failure, septic shock, and death.

AUTOPSY FINDINGS

The abdominal and thoracic cavities were opened, revealing a mild serous ascites, pleural and pericardium effusions. In the retroperitoneum, there were enlarged lymph nodes as well as a firm whitish mass involving soft tissue, both adrenal glands, and the adjacent renal capsule. (Figure 2) The visceral peritoneum showed numerous small whitish nodules over the stomach and colon. There was a whitish mass in pelvic topography involving the bladder wall, but preserving its mucosal surface. Both ovaries were enlarged by whitish tumor infiltration, measuring up to 10 cm. The uterus presented with endometrium and myometrium preserved.

The cervix showed an irregularity in the endocervical canal and transformation zone, with thickened wall, and a firm, whitish, endophytic tumor on the section surface. The microscopic examination evidenced a large cell, moderately differentiated, non-keratinizing squamous cell carcinoma measuring 1.5 cm in extension and 1 cm in depth, with an endophytic growing pattern. (Figure 3) There were also metastatic squamous cell carcinomas in the ovaries, fallopian tubes, bladder wall, peritoneal nodules, adrenal glands, and retroperitoneum lymph nodes.

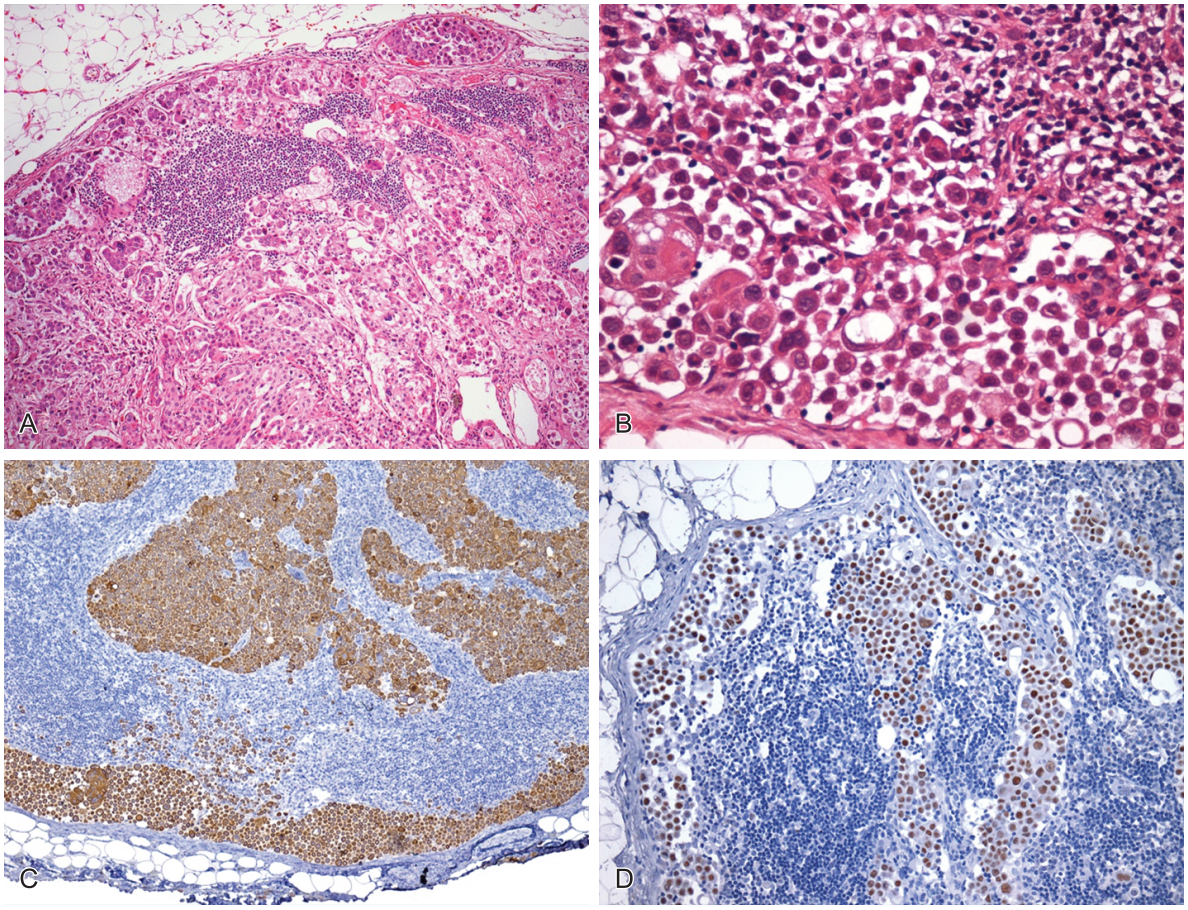

Figure 1 – Photomicrography of the lymph node **A -** (HE – 40×) metastatic squamous cell carcinoma; **B -** (HE – 400×) Neoplasic cells with vacuolated cytoplasm in the subcapsular sinus; **C -** (HE – 40×) Immunohistochemical study showing diffuse positivity for CK7 antibody; **D -** (HE – 100×) immunohistochemical study showing diffuse positivity for p63 antibody.

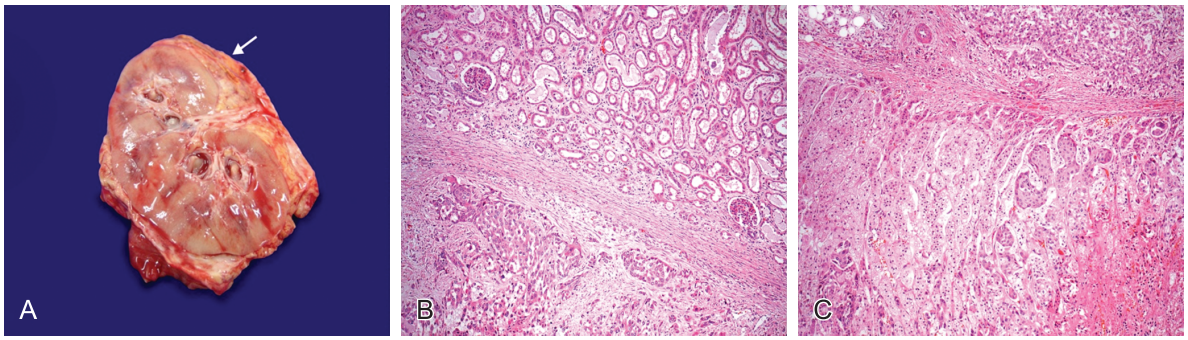

Figure 2 – A - Gross section of kidney and adrenal gland (arrow) with a hardened and whitish tissue involving the adjacent adipose tissue; **B -** Photomicrography of the kidney and adjacent tissue (HE – 100×) showing metastatic squamous cell carcinoma infiltrating the connective tissue adjacent to renal capsule; **C -** Photomicrography of the (HE – 100×) adjacent adipose tissue and cortical adrenal gland showing infiltration by metastatic squamous cell carcinoma.

The thoracic cavity revealed enlarged mediastinal and peri-esophageal lymph nodes. The esophageal wall was thickened. There were axillary and cervical enlarged lymph nodes, and a gray–whitish mass involving soft tissue of the left cervical region and the left lobe of the thyroid gland. Both mammary glands presented a firm, central, necrotic mass measuring up to 3 cm. The *vastus lateralis* muscle of the left thigh was also infiltrated by the mass. The microscopic examination revealed metastatic squamous cell carcinomas in each of these areas. (Figures 4 and 5)

The lungs were congested and heavy. Microscopic examination revealed diffuse alveolar damage and bronchopneumonia. (Figure 6) A

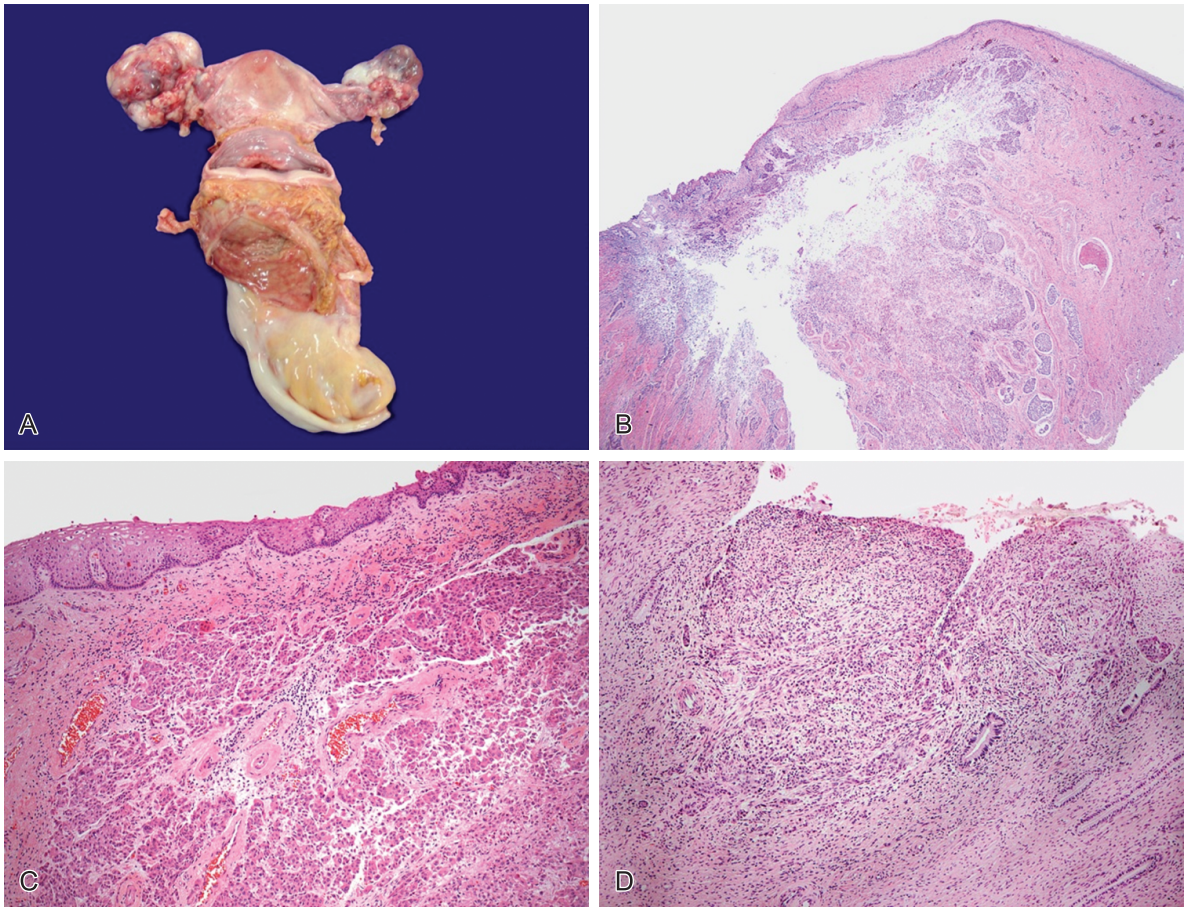

Figure 3 – A - Panoramic view of the enlarged ovaries involved by a whitish mass and the cervix with a slight irregular external orifice; **B -** Panoramic photomicrography of the cervix (HE – 25×) showing an endophytic growing pattern of the squamous cell carcinoma; **C -** Photomicrography of the cervix (HE – 100×) showing preserved ectocervical epithelium above the infiltrating cervical squamous cell carcinoma; **D -** Photomicrography of the cervix (HE – 100×) showing the endocervical mucosa involved by the cervical squamous cell carcinoma.

systemic finding of sepsis was observed in the spleen, represented by red pulp congestion and white pulp lymphoid hyperplasia in the microscopic examination.

No other significant gross or microscopic findings were detected.

Additional immunohistochemical analysis was undertaken in the previous cervical lymph node biopsy and the primary cervix tumor, revealing diffuse positive p63 immunophenotype in the tumor cells, compatible with squamous cell carcinomas.

DISCUSSION

Cancer of the uterine cervix is common worldwide and ranks second among all malignancies affecting women. In Brazil, it is the fourth leading cause of death in women, with an average of 4800 fatal cases per year. It is estimated that 17,540 new cases of uterine cervical cancer will be diagnosed in 2012.[1]

The colpocytology stained by the Pap test method is the screening test of excellence in assessing the degree of cellular alteration, able to detecting incipient lesions or those in the pre-malignant stage. Worldwide, the Pap test has been reducing the incidence of this neoplasia since its implementation.[2,3]

Both incidence and mortality from cervical cancer have sharply decreased after the adoption of well-run and periodically-performed screening programs using the Pap test.[4-6] In Iceland, the mortality rate declined by 80% for more than 20 years, and in Finland and Sweden by 50% and 34%, respectively.[4,7] Similar reductions have been observed in the United States and Canada. The decrease in incidence and mortality are proportional to the intensity of screening.[4,7]

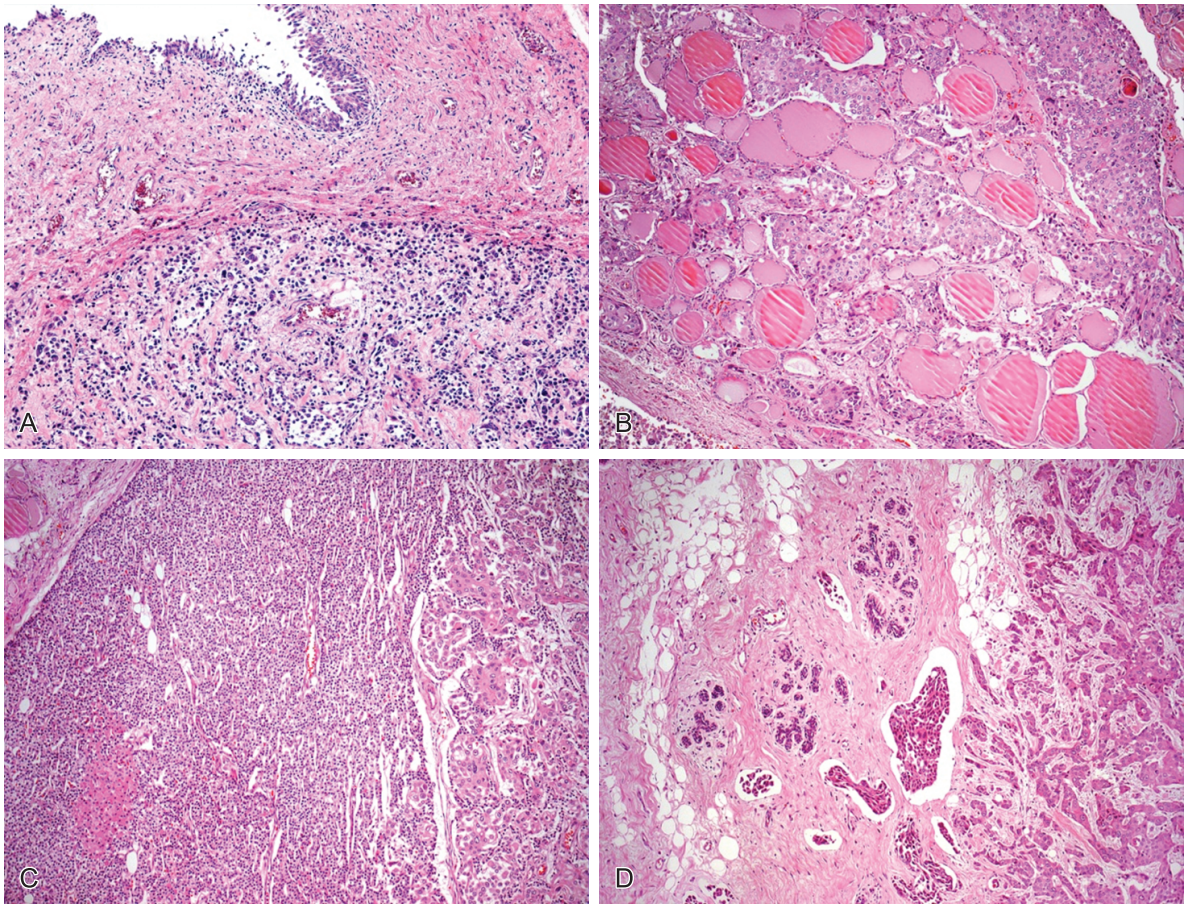

Figure 4 – A - Photomicrography of the bladder (HE - 100×) showing infiltration by metastatic squamous cell carcinoma; **B -** Photomicrography of the thyroid gland (HE – 100×) showing infiltration by metastatic squamous cell carcinoma; **C -** Photomicrography of the parathyroid gland (HE – 100×) showing infiltration by metastatic squamous cell carcinoma; **D -** Photomicrography of the mammary tissue (HE – 100×) showing infiltration by metastatic squamous cell carcinoma.

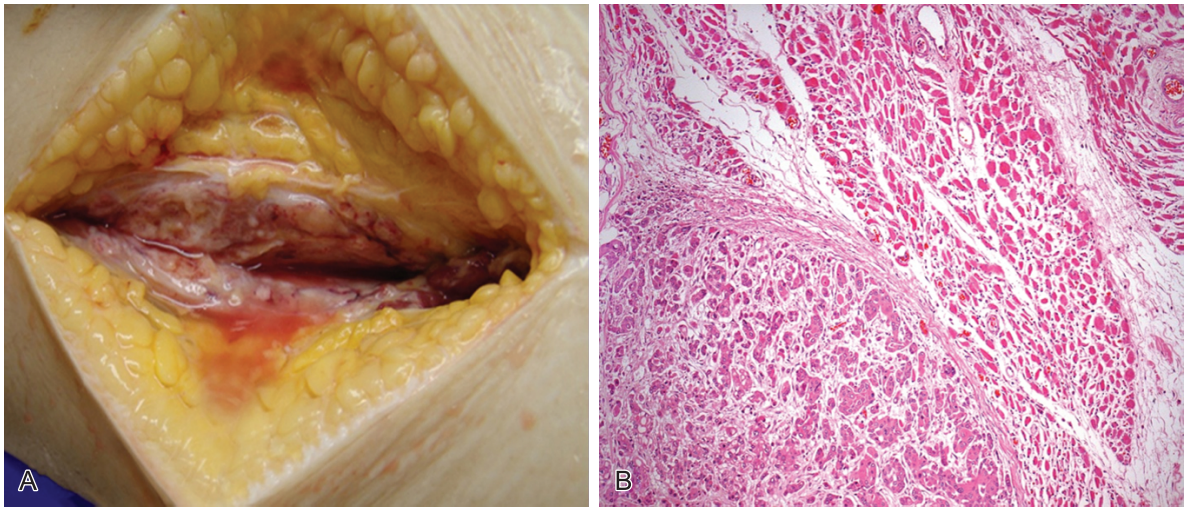

Figure 5 – A - Gross section of the left thigh showing a hardened and whitish tissue mass involving the muscle; **B -** Photomicrography of the skeletal muscle (HE – 100×) showing infiltration by metastatic squamous cell carcinoma.

Although relatively low cost, as well as being effective in early detection of cervical cell dysplasia, the Pap smear is criticized by the false-negative results. The range of this false-negative result varies between 6% and 68%.[8] The occurrence of errors during the slide preparation[9] and specimen fixation is not uncommon. Besides the possibility of cell overlapping and the presence of contaminant

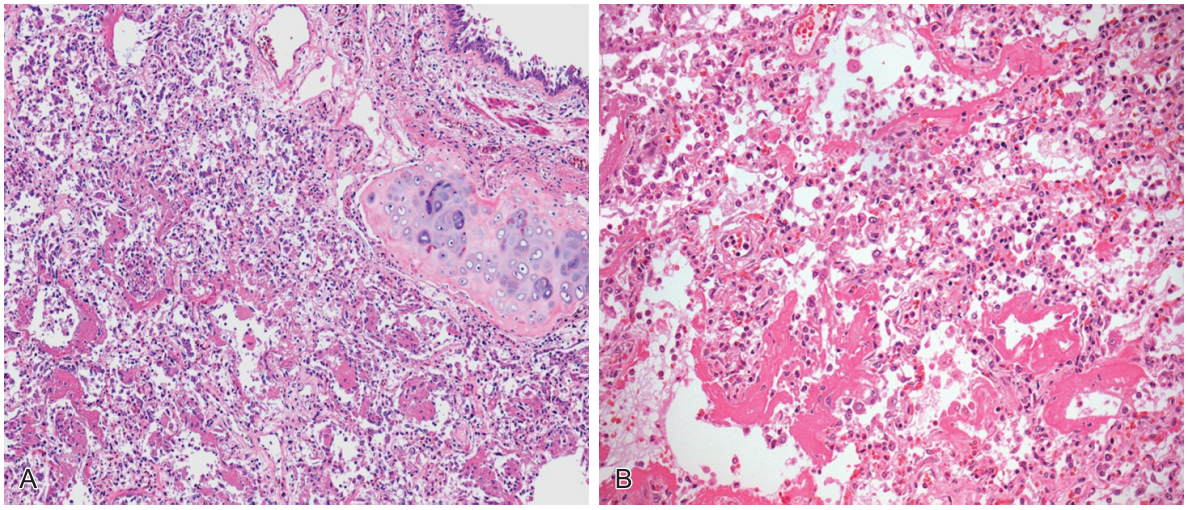

Figure 6 – Photomicrography of the lung. **A -** (HE – 100×) and **B -** (HE – 200×) showing deposition of fibrinous material in the alveolar wall and presence of macrophage and neutrophils into the alveolar lumen.

inflammatory cells hampering the cytologic evaluation, there is also the subjectivity and misinterpretation, mainly in overloaded laboratories. Felix et al.[10] called attention to the aberrant expression of E-cadherin in cervical intraepithelial neoplasia as being responsible for false-negative Pap smears. The persistence of these adhesion molecules throughout the entire epithelium interfere with the natural exfoliation of the dysplastic cells interfering with the diagnosis of the malignancy. The grade of dysplasia considered as the test threshold for positivity also interfere with the results.[11] Thus, a large sensitivity and specificity variation is observed, with the average of 58% (variation 11-99%) and 68% (variation 14-97%), respectively.[11-14] The patient of this report had an endophytic pattern of growth tumor, which had been reported to be often related to false-negative Pap smears.[15]

The gross features of a more advanced tumor depend upon its site of origin, the pattern of growth, and the rate of necrosis. Patients with an endophytic growth pattern tumor may exhibit a tumorless speculum examination. Some cervical cancers remain entirely within the endocervix presenting superficial normal epithelium. The underlying tumor becomes grossly or cytologically unapparent by colposcopy exam or Pap test. These endophytic tumors may produce a "barrel-shaped" cervix, which has a diameter greater than 4 cm.[16-18]

The rate at which invasive cancer develops from cervical intraepithelial neoplasia is usually slow, measured in years and perhaps decades.[19] This long natural history provides the opportunity for screening, which can effectively detect this process during the preinvasive phase, and thus allow early treatment and cure. However, the patient of this report seemed to present an "explosive" growth tumor, which became clinically evident in a very short period. These progressive and fast-growing cervical cancers are defined as cancers that have been diagnosed within 3 years of a last true-negative Pap smear.[16,20,21] Although they do not represent a specific entity based on any particular histology, some authors have shown that this condition occurs more often in younger women, with a higher incidence of adenocarcinomas or adenosquamous carcinomas. Progressive and fast-growing cervical cancer could represent cases with a false-negative Pap smear in which the endocervical component had not been adequately screened. In these cases the endocervical and the ectocervical squamous epithelium may be normal by cytological, histological, and colposcopy examinations. The nature of the cancer becomes apparent only when the tumoral cells reach the overlying surface.[16]

Most cervical cancers arise from human papillomavirus (HPV) infected cells. The Infection by HPV (sexually transmitted) behaves transiently in most cases, with spontaneous clearance in more than 80% of infected women within 1-2 years, especially in adolescents and young adults.[22] Epidemiological studies have shown that despite the high prevalence of HPV infection in sexually active women, only a small portion of them, infected by oncogenic types, will progress to high grade squamous intraepithelial lesions and cancer of the cervix. The persistence of HPV infection (particularly by types 16 and 18) is closely involved in the process of cervical carcinogenesis and is considered the strongest risk factor for the emergence of pre-malignant lesions of the cervix.[23-26] Despite the evidence showing the important role of HPV infection in the pathogenesis

of cervical cancer, other agents and cellular events still need to be determined, since most women with a cervical HPV infection never develop cervical cancer. [27]

A young age at first intercourse, an increasing number of sexual partners, and multiparity increase the risk of cervical cancer.[28,29] The International Agency for Research on Cancer (IARC) reported that women with seven or more term pregnancies had a higher risk of developing cervical cancer compared with nulliparae.[30] The risk for developing squamous cell carcinoma of cervix is two times higher in smokers and is closely related with prolonged use and the daily number of smoked cigarettes.[29-31] The association between oral contraceptive use and the risk in developing cervical cancer is still controversial.[32-35]

Among the histological types, the squamous cell carcinoma accounts for 80-85% of all cancers of the cervix (ectocervix).[29,36] Adenocarcinomas represent 10-15% of cancers and originate from the mucous secreting endocervical glandular cells. The mixed carcinomas, neuroendocrine tumors, sarcomas or lymphomas are more rare.[36] Regarding the immunohistochemical examination, it is important to remember that squamous cervical carcinoma can present an immunophenotype with positive cytokeratin 7 (CK7) and carcinoembryonic antigen (CEA) antibodies. The hormonal receptor ER and PR show decreased expression in cervical intraepithelial neoplasia and negative for invasive squamous cervical carcinoma.[37-40] Those findings can lead to the misdiagnosis of adenocarcinoma, especially in poorly differentiated tumors. Although CK7 and CEA antibodies were usually related to adenocarcinomas of other anatomic sites (e.g. lungs), they could also be expressed in squamous cervical carcinoma in 87% and 57-90%, respectively. In metastatic disease, it is worth adding the antibody p63 in the immunohistochemical panel. This antibody is a p53 homologue gene involved in the development and maintenance of stratified epithelium, and because of that it is a useful antibody in the identification of myoepithelial and squamous cell carcinomas.[41-42] In the female genital tract, p63 is expressed in the basal and parabasal layers of mature cervical, vaginal, and vulval squamous epithelium, and is useful to establish the diagnosis of cervical squamous cell carcinoma.[43] In the revision of the case, the p63 antibody was added to the immunohistochemical panel, which showed a diffuse pattern of positivity. This way it was possible to exclude the diagnosis of adenosquamous carcinoma or poorly differentiated adenocarcinoma in the previous cervical lymph node biopsy.

The cervical cancer typically spreads to adjacent structures by contiguity. Pelvic and para-aortic lymph nodes are involved by lymphatic dissemination, and less frequently liver, lungs, and bones are involved by hematogenic dissemination.[44]

Metastases to the breast, adrenal, brain, or muscles are very rare. Chura et al.,[45] in a review of 1560 cases of patients with carcinoma of the cervix, found 12 cases with brain metastasis. Baron et al.[46] described a case of cervical cancer in the remnant cervix of a patient who underwent subtotal hysterectomy. In this case, metastases were found in both adrenal glands. Metastases to the breast have been reported in clinical and autopsy reports. Badib et al.[47] found four cases of breast metastases among 278 autopsied patients with cervical cancer. The reported frequency of this metastatic site is 0.5-6.6%.

The first description of muscle metastasis was reported by Wittisch in 1854.[48] In 1989, Stephen Paget[49] also observed that skeletal muscles were rarely the site of tumor metastasis. After Wittisch's observation, until 1991 only 242 cases of muscle metastasis were reported in 82 publications.[50] The exact incidence of skeletal muscle metastases is barely known since they can evolve without symptoms, they may not exhibit a clinically detectable size, they can not be detected by positron emission tomography or CT scan, and cancer-related deaths are not routinely autopsied. Even so, contemporary studies show metastatic muscle involvement in less than 1% of all malignancies, despite the rich muscle blood supply and the high percentage (nearly 50%) of the total body weight represented by the muscle mass.[51] When muscle metastases occurs, it is generally associated with melanoma, lung, genitourinary, and gastrointestinal cancers. Menard and Parache,[50] in a retrospective study of cancer patients seen between 1980 and 1990, found only seven cases of metastases to skeletal muscles, but in no cases was the cervix the primary tumor site.[51] The rarity of muscle metastases may be justified by its contractile activity, local change in pH, toxic-free radical oxygen, accumulation of lactic acid, blood flow per unit weight (mL/min/kg), intramuscular blood pressure, and local temperature.[48,52-55] Sudo et al.[56] also consider the activity of protease inhibitors located in the basement membrane, and antitumor activity of lymphocytes and/or natural killer cells within the

skeletal muscles. In vivo evidence supports that skeletal muscle peptidic factors may influence the metastasizing process.

In 2006, Ferrandina et al.[51] found eight cases of cervical cancer with metastases to skeletal muscle, adding a new case report in their review. Among these nine cases, eight were histological squamous cell carcinomas and one small cell carcinoma. In 2010, Karunanithi et al.[57] published another case of carcinoma of the cervix with metastasis to striated muscle, and in 2012, Tamam et al.[58] reported a case of squamous cell carcinoma with metastasis to subcutaneous tissue and various muscle groups. The most affected muscle groups were the psoas and Iliopsoas, but involvement of the biceps, deltoid, masseter, intercostal, buttock, thigh muscles, and abdominal wall were also reported.[59-60] All cases of striated muscles metastasis occur in the context of advanced disease or immunocompromised patients, resulting in the observed poor prognosis.[50] The diagnosis of muscle metastases can be difficult mainly when asymptomatic, but in most cases they are palpable and painfull.[50]

CONCLUSION

This report calls attention to the dramatic and extensive presentation of cervical cancer, considering this histological type. Moreover, the patient of this case report followed the screening program. Even after a thorough investigation, the primary tumor could not be diagnosed, representing a dramatic and challenging situation in clinical practice.

It should be expected that maladies such as cancer of the cervix, which offers the possibility of early detection and consequently the possibility of a cure, if covered by a governmental program for prevention, would never reach such an outcome. We wondered what was at fault for the misdiagnosis. The endophytic pattern of growth probably led to the atypical natural history of this case. The normal speculum gynecological examination and the pattern of the metastases certainly contributed to the unaccomplished diagnosis.

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Correspondence: Divisão de Clínica Médica
Av. Prof. Lineu Prestes, 2565 – Cidade Universitária – São Paulo/SP – Brazil
CEP: 05508-000 – Phone: +55 (11) 3091-9200
E-mail: ffcampos@usp.br