Cervical adenocarcinoma generator of procoagulant status and ischemic stroke

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Abstract

The procoagulant status of neoplastic patients is well known in medical literature, but in the last years there is attempted a correlation between the histological types of neoplasia and the risk for thrombotic strokes. We present the case of a 44-years-old patient undergoing early menopause, who was diagnosed with cervical tumor of the serous adenocarcinoma type. The patient underwent external radiotherapy, and, in the seventh day of treatment, she suffered a frontal-temporal-parietal ischemic stroke with left hemiplegia. The blood testing highlighted procoagulant products (double fibrinogen compared to normal values, deficit of antithrombin and a high number of thrombocytes). The patient received neurological and rehabilitation treatment, at first with Heparin, followed by the administration of an antiaggregant. During this treatment, the deficit remained unchanged. She continued the neurological and rehabilitation treatment, followed by radiotherapy, with a good evolution. Six months after the stroke, it was decided the surgical tumor ablation of cytoreduction. The post-surgery histological examination highlighted specific changes due to post-surgery radiotherapy, without the presence of any neoplastic cells. The imagistic evaluation, computed tomography (CT) every three months after surgery, did not highlight any suggestive dissemination elements. The occurrence of an ischemic stroke in a patient with endocervical neoplasm of the adenocarcinoma type during radiotherapy imposed the discharge of chemotherapy, with subsequent imaging, biological and histopathological monitoring after surgery. The cause of stroke in this case is determined by the hypercoagulant status in the context of the developed neoplasia, the patient being free of any other risk factors.

Keywords: stroke, endocervical adenocarcinoma, radiotherapy, ischemic stroke.

Introduction

Cervical cancer is known as the third cause of cancer regarding frequency in women. World Health Organization (WHO) established three types of epithelial tumors of cervical cancer, as far as the histopathological aspect is concerned: squamous, glandular (adenocarcinomas), undifferentiated and neuroendocrine carcinomas of the epithelial tumor type. Among these, adenocarcinoma represents 10–20% of cervical invasive carcinomas, and 70% are of the endocervical type [1]. Invasive glands have a variable arrangement, thus the tumors have a papillary aspect, more or less emphasized [2].

The occurrence of ischemic stroke in patients with endocervical adenocarcinoma is well-known in medical literature as an additional risk factor in general population, the risk being higher if the age is less than 51 years old [3].

There is a correlation between coagulation disorders in the neoplastic patient, known as the Trousseau’s syndrome, but it seems that the adenocarcinoma may promote more than a migratory thrombophlebitis, and it may take various aspects, even dramatic ones by developing a risk for ischemic stroke with an immediate vital risk.

It seems that the risk for suffering a stroke in the neoplastic patient is underdiagnosed, therefore there are quoted cases between 26–40% of the patients with ischemic stroke lesions, without the detection of another determining cause, the so-called cryptogenic stroke [4].

Apart from this aspect, even the neoplasm treatment itself can be a cause of hypercoagulation status, with cases of stroke after radiotherapy, the cases being more frequent especially when this was performed at head and neck level [5].

The relation between cancer and stroke is approximated at about 15% of the neoplastic patients, regarding the incidence, with only 50% being diagnosed. The risk is higher as certain procoagulant and inflammatory biological parameters are present: antithrombin deficit, N-terminal pro-brain natriuretic peptide (NT-proBNP), D-dimers, creatine phosphokinase from cardiac muscle (CPK-MB), high C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen [6].

We present a rare case of a patient with a neoplastic profile, known with cervical adenocarcinoma, who suffered a stroke during radiotherapy. This case brings back into discussion the procoagulant status of the adenocarcinoma.
with the occurrence of thrombotic strokes, some severe ones, as observed in this patient. The ischemic stroke suffered by our patient led to the onset of a hemiparetic motor deficit that required a rehabilitation treatment in several stages. The histological type of the neoplastic tumor is discussed and compared within present casuistry in literature, including the correlation with the risk for severe thrombotic strokes.

Case presentation

In September 2016, L.D. patient, aged 44 years old, presented to the Clinic of Neurological Rehabilitation, Neuropsychiatric Hospital of Craiova, Romania, for the rehabilitation of the motor deficit in the left half body part, as a result of an ischemic stroke suffered on August 8, 2016, with a hospitalization period between September 22–October 7, 2016.

The medical history recorded an early menopause at 42 years old, two pregnancies with term delivery, eutrophic newborns, an abortion at request, with no other medical events. The patient presented repeated metrorrhagias in June 2016. She was examined gynecologically and there was performed a cytological Babes–Papanicolaou test. The cytological result highlighted the presence of atypical glandular cells, an aspect suggesting the presence of a neoplasia (Figure 1, A and B). The cytological examination highlighted glandular-type cells arranged in groups or placcards, rare, isolated, with hypertrophic nuclei, oval-shaped, with stratifications, nuclear hyperchromasia, irregular contour, high nuclear/cytoplasmic ratio. There was recommended the performance of a cervix biopsy and there was established the diagnosis of a possibly serous endocervical adenocarcinoma (Figure 2, A and B).

The anatomopathological result of the biopsy fragment highlighted tumor formations with a papillary aspect and complex ramifications, a conjunctive–vascular axis lined up with stratified tumor cells, marked cellular and nuclear pleomorphism, atypical mitoses, papillary buds. The anatomopathological aspect imposed a differential diagnosis with the endocervical villoglandular adenocarcinoma, the serous endometrial or ovarian carcinoma with cervical extension. For the certainty of diagnosis, there was recommended an immunohistochemical (IHC) examination. Carcinoembryonic antigen (CEA) is known as an important marker for the confirmation of neoplasia. There were performed various IHC markers of the type CA125 and CEA (Figure 3, A and B), Ki67 and p53
(Figure 4, A and B), IHC markers for the hormonal estrogen and progesterone receptors (ER and PR) (Figure 5, A and B), CK5/6 and CK7 cytokeratins (Figure 6, A and B). There was identified an intensely positive epithelial immunoreactivity, both nuclearily and/or cytoplasmatically for CA125, CEA, Ki67, CK5/6, CK7, and an estrogenic one (ER), respectively. The correlation between the clinical examination and the histopathological and IHC one established the diagnosis of endocervical adenocarcinoma with a serous pattern of papillary type.

Figure 3 – (A) Intensely positive nuclear and cytoplasmic CA125 in the papillary epithelium (Immunomarking with anti-CA125 antibody, ×200); (B) Intensely positive nuclear and cytoplasmic CEA in the papillary buds (Immunomarking with anti-CEA antibody, ×200). CEA: Carcinoembryonic antigen.

Figure 4 – (A) Moderately positive nuclear Ki67 (Immunomarking with anti-Ki67 antibody, ×200; (B) Focal positive nuclear p53 (Immunomarking with anti-p53 antibody, ×200).

Figure 5 – (A) Intensely estrogenic, nuclear positivity in the papillary epithelium (Immunomarking with anti-ER antibody, ×200); (B) Moderate progesterone stromal positivity (Immunomarking with anti-PR antibody, ×200). ER: Estrogen receptor; PR: Progesterone receptor.
Following examination, the oncologist recommended and started radiotherapy. Taking into consideration the patient’s age and the histological type of the endocervical tumor, there was decided a symptomatic 20 Gy radiotherapy in five fractions. During the last radiotherapy session, in August 2016, the patient suffered a massive ischemic stroke, with the onset of a left hemiplegia, homolateral hemianopsia, being transferred to the Clinic of Neurology. The computed tomography (CT) examination described a heterogeneous hypodense area with an aspect of acute ischemic frontal-insular-parietal-p aerial lesion, with a medial extension at the level of the external capsule and the semiolateral center, a Sylvian distribution territory with a minimum left deviation of the pellucid septum. An aspect of a relative hyperdensity of the M1 segment and insular aspect of the right medial brain artery, with flow reduction were also observed, as well as small hypodense areas of the right parietal and occipital regions. The fourth ventricle without deviation on the medial line. The magnetic resonance and magnetic angioresonance examination performed in August 17, 2016, showed a temporal right insular cortical-subcortical region, a subacute ischemic lesion and cytotoxic edema in the cortical gyriuses, in the superficial territory of the right medial brain artery, with an aspect of hyalinization and microcalcifications, areas of simple glandular hyperplasia (Figure 8A), including glands, partly dilated cystically, with irradiation changes, areas of xanthomatous cells and microcalcifications, hyalinized vessels and immature squamous metaplasia of the lining epithelium, aspects that were also confirmed by the immunohistochemical investigations (Figure 8B; Figure 9, A and B; Figure 10, A and B).

The patient continued the oncological treatment with external photon beam radiotherapy on a target volume, the pelvis area, the “box” technique in total dose (TD) of 20 Gy, 2 Gy per day in 10 fractions, between September 8–22, 2016, a well-tolerated clinically and hematologically irradiation. The brachytherapy radiotherapy stage, two applications with a total dose of 1500 Gy and three more October 18–November 2, 2016, with a TD of 2250 Gy.

The imagistic evaluation, CT of the thorax, abdomen and pelvis did not highlight any pathological images with an evolving pattern, maximum 1 cm adenopathies with a reactive aspect, without any contrast settings present (Figure 7, A and B). The case evolution with the development of an ischemic stroke impeded the natural oncological treatment progression, and it was not until December 2016 that there was performed a lymphadenectomy Wertheim type and extended exploratory laparotomy. The anatomopathological result of the surgical ganglionary piece showed an aspect of hyalinization and microcalcifications with post-oncological treatment changes and ganglions with reactive follicular hyperplasia. On the hysterectomy piece, namely the cervix, there were highlighted: in the exocervix, an epithelium with ulcerative areas and low-degree dysplasia, intense fibrosis area and lymphoplasmocytary inflammation; in the endocervix, a fibromatous structure including glands, partly dilated cystically, with irradiation changes, areas of simple glandular hyperplasia (Figure 8A), extended area with xanthomatous cells and microcalcifications, hyalinized vessels and immature squamous metaplasia of the lining epithelium, aspects that were also confirmed by the immunohistochemical investigations (Figure 8B; Figure 9, A and B; Figure 10, A and B).
The oncological evaluation in February 2017 showed a post-surgery and post-radiotherapy and brachytherapy status, and at abdominal and pelvic CT examination there were highlighted the calcified iliac ganglions. In this case, there is recommended a radiotherapy control for a possible new stage of treatment.

In March 2017, the patient presented for a new treatment stage of neurological rehabilitation, still she accused intense headache that did not respond to any conservative therapy, increase of spasms, balance disorders. The CT brain investigation highlighted changes suggesting an old frontal-temporal-parietal and occipital ischemia of large sizes 9.5/3.5 cm inside the right MCA and right Sylvian area, with the ventricular system traction, without any tumoral contrast settings (Figure 11, A and B).

Figure 7 – (A and B) Postcontrast computed tomography (CT) of axial sections: uterus with visible cavity, heterogeneous diffuse cervix. Investigation by stage for an underlying disease, by native and postcontrast CT, oral and intravenous, not showing any lung or abdominal-pelvic secondary determinations; also, there are not observed any adenopathies; only in the cervix, there may be observed a heterogeneous structure, probably as a secondary effect of radiotherapy.

Figure 8 – Glandular-cystic hyperplasia: (A) HE staining, ×200; (B) Negative immunoreactivity for CEA (Immunomarking with anti-CEA antibody, ×200). HE: Hematoxylin–Eosin; CEA: Carcinoembryonic antigen.

Figure 9 – (A) Negative immunoreactivity for Ki67 (Immunomarking with anti-Ki67 antibody, ×200); (B) Negative immunoreactivity for p53 (Immunomarking with anti-p53 antibody, ×200).
Figure 10 – (A) Estrogenic stromal positive immunoreaction (Immunomarking with anti-ER antibody, ×200); (B) Poorly positive progesteronic stromal immunoreaction (Immunomarking with anti-PR antibody, ×200). ER: Estrogen receptor; PR: Progesterone receptor.

Figure 11 – (A and B) Native CT of axial sections. It is observed a hypodense area with sequelae aspect in the island lobe, with a right frontal-parietal cranial extension, with asymmetric dilatation and minimum tracting of the right lateral ventricle. CT: Computed tomography.

In all this time, there were controlled the procoagulant markers, which preserved themselves constantly within the normal range, with the presence of the hypercoagulant status only at the cervical neoplasia diagnosis moment.

**Discussion**

The relation between the onsets of thrombotic phenomena in the neoplastic patients is known for almost 150 years, when Trousseau described in 1865 a migratory thrombophlebitis in the patients with gastric neoplasm.

In 1985, Graus et al. published a study on a necrotic analysis of the patients with diagnosed neoplasia and observed that 14.6% of them had signs of cerebrovascular disease, even though only 7.1% presented clinical signs [7].

The cytological Babes–Papanicolau test introduced since 1950 and recommended by the American Association for Cancer is advocated starting from the age of 21 years old, having a sensitivity of 75–98% and a specificity of 98–100%, thus reducing the cervix cancer incidence by 79% and mortality by 70% [8, 9].

The physiopathology of generating thrombotic phenomena in the neoplastic patients is conditioned by the histological type of the tumor, the extension degree and the received treatment. Neoplastic cells are direct thrombin generators and, secondarily, the local tissue reactivity has a procoagulant effect as a response to the tumor. The tumor procoagulant was found in the malignant structures, but not in the normal ones, being a calcium-dependent cysteine protease. This directly activates the X coagulation factors.
Particularly, some adenocarcinomas are mucin producers [10] that interact with leukocytes and thrombocytes and generate thrombocytarian microthrombi.

The biological investigation is important, as it is the one that may confirm the procoagulant status. Thus, there is necessary to be determined the prothrombin index, fibrinogen, D-dimers, number of thrombocytes, antithrombin levels. There should be specified that these tests may also be changed in the patients with liver diseases or liver metastases, or with medullar suppression after chemo-radiotherapy.

The presented case was included in the procoagulant pattern of neoplasia with biological paraclincal elements specific to the procoagulant status. When the ischemic event occurred, the patient presented high inflammation markers, double values for fibrinogen, three times higher CRP values, antithrombin deficit, present D-dimers, low prothrombin index, high number of platelets. These values came back to normal after a period of approximately two months, with the persistence of normal values during the specific treatment period. This aspect certifies that the ischemic stroke coexisted with a procoagulant moment, the patient being recently diagnosed with endocervical neoplasia. The diagnosis was difficult, being imposed by an abnormal cytology that determined the performance of a cervical biopsy. The probability for a cervix serous carcinoma, as a rare variant of this type of carcinoma, required immunohistochemistry for a certain and differential diagnosis [11]. The association of nuclear and cytoplasmic carcinoma, as a rare variant of this type of carcinoma, required immunohistochemistry for a certain and differential diagnosis [11]. The association of nuclear and cytoplasmic carcinoma, as a rare variant of this type of carcinoma, required immunohistochemistry for a certain and differential diagnosis [11].

In the present case, the treatment leading to disappearance of neoplastic lesions and control of procoagulant factors shows that the procoagulant status was found only at the onset, and following the applied treatment and the stroke there were not observed any other prothrombotic generating factors.

Another study, published in 2012, of Christopher Jan Schwartzbach of the University of Mannheim, Germany, assessed 140 patients diagnosed with cancer. This proves that the onset of an ischemic stroke is highly underdiagnosed in various vascular areas, and the D-dimers are frequently high compared to the control group (140 patients) where risk factors like high blood pressure and diabetes were much higher. This study confirmed the existent hypercoagulation state in the patient with neoplasia and high risk for stroke in the absence of other risk factors. The authors consider that the hypercoagulation status manifests by the onset of thrombotic phenomena in various vascular areas, which was also observed in the case of our patient who presented extended ischemia in the Sylvian area and in the right medial brain artery with clamping of distal vessels [18].

They studied the data provided by Robert Koch Institute and Society for Epidemiological Cancer Registry in Germany (Robert Koch-Institut und die Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V.), where there was observed that lung and pancreas neoplasias were involved more often. It is well known that histologically these neoplasias are mainly of the adenocarcinoma type [18, 19].

In a recent publication, in 2014, they start from the idea of an existing hypercoagulability state in neoplastic disease and evaluate the risk for suffering a stroke. They bring into discussion the possibility that present investigations may not associate ischemic stroke in neoplastic patients strictly with the hypercoagulation status, yet a cryptogenic stroke, which cannot be clarified at present moment. In conclusion, their study showed that 3% of the total of strokes occurs in a neoplastic context.

The case of our patient does not fit into the cryptogenic type, having the proof of present hypercoagulation state, the discussion being on the cause of this status, whether the ischemic event has also existed prior to the diagnosis of neoplasia.

Based on the history of the patient, there were no clinical and biological elements of previous thrombophilia, no suspicions of antiphospholipid syndrome, latter excluded by specific blood determinations, or other pathogenic situations with procoagulant setting. Thus, the main cause of the ischemic stroke was the hypercoagulation brutally occurring in association with adenocarcinoma [3].

The present case excluded the treatment causality, as the radiotherapy was not applied in risk areas, and there is not a time factor from its initiation. The stroke onset was caused by the neoplasia-induced hypercoagulation status of the patient with no other causes for this state, the more so as the subsequent hypercoagulation profile assessment was within normal limits.
Conclusions

Our case confirmed the fact that malignant tumors favor a hypercoagulant status, generating ischemic strokes by specific mechanisms in the neoplastic patients and it is dependent on the histological type of neoplasia. Adenocarcinoma is by far the most aggressive also due to the hypercoagulation reactions by generation of multiple thrombotic events, some being severe, with vital risk, like in the presented case. Although it seems a classical one, this case brings into discussion a problem of thrombotic events succession: disease or treatment, where the prognosis this case brings into discussion a problem of thrombotic in the presented case. Although it seems a classical one, thrombotic events, some being severe, with vital risk, like the hypercoagulation reactions by generation of multiple Adenocarcinoma is by far the most aggressive also due to it is dependent on the histological type of neoplasia.

Conflict of interests

The authors declare that they have no conflict of interests.

References


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