INFLAMMATORY PSEUDOTUMOR OF THE CERVIX: CASE REPORT AND REVIEW OF THE LITERATURE

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SUMMARY – The third recorded case of inflammatory pseudotumor of the cervix is reported. Inflammatory pseudotumor is considered to be a benign, self-limited lesion of obscure etiology. The condition is thought to be related to an unusual tissue response to injury, past infection and autoimmune disorders. Although extremely rare at this site, inflammatory pseudotumor should be considered in the differential diagnosis of a mesenchymal lesion or tumor-like inflammatory and reparative-like lesion. In December 2003, an 18-year-old nullipara presented to our hospital for dysfunctional bleeding. A solitary leiomyoma-like growth measuring 4.2x3.8 cm, originating from the cervix, was incidentally found on gynecologic examination. The tumor was surgically excised. Samples were stained by H&E, Gomori, pancytokeratin, vimentin, smooth muscle actin, myoglobin, desmin, S-100, CD-68, Factor VIII and p53. Microscopic evaluation of H&E samples showed a distinctive mesenchymal lesion composed of spindle cells displaying morphological features of myofibroblasts, fibroblasts and histiocytes mixed with a considerable number of inflammatory cells. Immunohistochemical analysis showed positive reaction to vimentin, smooth muscle actin, myoglobin, CD-68, and some tumor cells were unexpectedly positive for S-100. Gomori and Factor VIII emphasized the reticulin/capillary network. Three years after excision of the inflammatory pseudotumor of the cervix with no histologic evidence of malignancy, the patient is feeling well with no signs of relapse. In this as well as in other similar cases we suggest long-term follow up.

Key words: Cervix disease – pathology; Cervix disease – immunohistochemistry; Plasma cell granuloma – pathology; Case report

Introduction

Recently it has been recommended to use the term inflammatory myofibroblastic tumor for lesions called inflammatory pseudotumor (IPT), plasma cell granuloma, omental mesenteric myoid hamartoma and inflammatory fibrosarcoma. The considerable morphological and clinical overlaps combined with both clinical and genetic evidence of their neoplastic nature led to the unification of these entities¹. The use of the term inflammatory pseudotumor is now of historical significance, yet being most descriptive.

IPT has become an almost ubiquitous tumorous condition. It occurs mainly in children and adolescents with a slight female predominance. Tumor size depends on the site, most often in the 5-10 cm range. There is recent evidence of the possible multifocal localization and even congenital recurrence². Curiously enough, overall local recurrence develops in 14% of patients between three months and seven years. IPTs not confined to a single organ have an even higher chance of recurrence, especially if localized in the lungs (46%). Single organ IPT and adequate excision decrease recurrence to 1.5% and 8% in pulmonary and extrapulmonary IPT, respectively³. Metastatic disease, recorded in less than 5% of cases, can hardly be predicted on morphological grounds. According to some authors, cases with clearly atypical cytomorphology can be regarded as malignant⁴.
The condition is thought to be related to an unusual tissue response to injury, past fungal or Epstein-Barr virus (EBV) infection, and autoimmune disorders. Although asymptomatic in many cases, the most frequent clinical symptoms include fever, night sweats, fatigue, lymphadenopathy, leukocytosis, hypogammaglobulinemia, erythrocyte sedimentation, weight loss, hypochromic anemia in IPT cases localized in the uterus, and symptoms secondary to the presence of the tumor.

During the past five years, more than two hundred cases of IPT have been described. They were mostly localized in the lungs, liver or spleen, not so often in the kidney, bladder, orbit or central nervous system, seldom in the pancreas, parotid gland, ureter, larynx or lymph nodes, and rarely in the testes, stomach or intestines. There are some unique cases dealing with the epidermal space of the thoracic spine, ethmoid sinus, trigeminal nerve, diaphragm, and there are IPTs of cutaneous, oral or pituitary localizations.

We report on the third recorded case of IPT of the cervix\textsuperscript{12,13}. Only seven previously described cases deal with IPT of the uterus\textsuperscript{12-14}.

**Case Report**

In December 2003, an 18-year-old nullipara presented to Dr. Ivo Pedišić General Hospital for dysfunctional bleeding. The patient reported no genitourinary, gastrointestinal or respiratory complaints. Her menstruation had been regular up to two weeks before the examination. During the preceding three years she was taking oral contraceptives. She reported no trauma or induced artificial abortion in her history.

A solitary leiomyoma-like growth measuring 4.2x3.8 cm, originating from the cervix was incidentally detected on gynecologic examination. The dimensions and site of the lesion were confirmed by ultrasound.

Surgical extirpation of the tumor was performed while preserving the rest of the uterus. According to the gynecologist performing the operation, the tumor could not be evacuated as easily as expected. Tumor mass seemed to have in part infiltrated the posterior wall of the cervix. The majority of the lower cervix was extirpated accordingly.

The operatively obtained specimen was paraffin embedded and 5-μm sections were stained by standard H&E and special histologic Gomori stain. In order to achieve definitive diagnosis the material was subsequently analyzed by the special histologic Gomori technique and an immunohistochemical palette consisting of pancytokeratin (Dako; 1:50), vimentin (Dako; 1:200), smooth muscle actin (SMA) (Dako, 1:125), myoglobin (Dako; 1:300), desmin (Dako; 1:50), S-100 (Dako; 1:300), CD 68 (Dako; 1:75), Factor VIII (Dako; 1:25) and p53 (Dako; 1:25). Positive expression was analyzed descriptively and semiquantitatively.

**Macroscopic examination** proved to be difficult because the pathologist had to examine the tumor in pieces measuring from 0.7 to 4.5 cm in diameter. The cut surface of the tumor was solid, whorled and white-yellowish, with hemorrhage and necrosis areas. The border between the tumor and healthy cervix was indistinct.

**Microscopic evaluation** of distinctive mesenchymal lesion composed of spindle cells displaying morphological features of myofibroblasts, fibroblasts and histiocytes mixed with a considerable number of inflammatory cells revealed a biphasic pattern of tumor cells. The predominant population of mildly atypical but mitotically inactive spindle cells was arranged in interlaced fascicles sometimes growing in a focal whirling pattern within the polymorphous inflammatory infiltrate, mainly consisting of plasma cells and foamy histiocytes, while lymphocytes and neutrophils could be seen in smaller or larger clusters depending on different HPFs (Figs. 1 and 2). Some nuclei seemed to be plump and vesicular. The mass lacked the capsule and the border with the scant tissue of the uninvolved portion of the cervix was ragged.

**Immunohistochemical staining** showed positive reaction to vimentin, SMA, myoglobin, CD-68 and S-100.

![](image1)

*Fig. 1. Inflammatory pseudotumor of the cervix (H&E, X100).*

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The cytoplasm of spindle cells showed diffuse and moderately to strongly intensive (+/++++) golden-brown positive reaction to vimentin, SMA (Fig. 3) and myoglobin. Some rare tumor cells that looked like spindle cells showed dusty golden, moderately intensive (+) reaction of cytoplasm to S-100. The inflammatory infiltrate was positive for CD-68 but recognized only histiocytes with light brown, granular, diffuse and strongly intensive (++++) cytoplasmic reaction (Fig. 4). Pancytokeratin, desmin and p53 showed no expression in tumor samples. Factor VIII and Gomori emphasized the capillary IPT network, but tumor cells were negative.

Discussion

The term IPT was first introduced in 1939 by Brunn who described two lung tumors\(^\text{18}\). Its modern name which implied and linked inflammatory etiology and tumorous mass was introduced in 1954 by Umiker and Iverson\(^\text{19}\). The lungs are the usual location but recently there are an increasing number of reports of extrapulmonary sites with liver as the most common site. Nevertheless, IPT of any origin is considered to be a benign, self-limited lesion of obscure etiology which involves evidence supporting both infective and neoplastic processes.

There are many reports which associate IPT with *M. avium intracellulare*, *C. jejuni*, *B. sphaericus*, *C. burnetti*, EBV and *E. coli*. Most recently, Navai *et al.* have described IPT of the testes as part of an acute retroviral syndrome\(^\text{20}\). Association of IPT and previous abdominal surgery, trauma, peritoneal shunt, radiotherapy, steroid usage, and some genetic factors has also been reported\(^\text{21}\).

According to some authors, EBV is detectable in a large number of spindle cells in 66.7% of hepatic and 50% of splenic IPTs\(^\text{22,23}\). Spindle cells in cases of IPT are often interpreted as but not proven to be myofibroblasts. The finding of EBV in actin-positive spindle cells might suggest a similarity to EBV-positive smooth muscle tumors\(^\text{22,23}\). As most positive EBV tumors are localized in the liver and spleen, Chan considers them different from the IPT of organs and proposes the term IPT of follicular dendritic cell type\(^\text{24}\). However, Chan *et al.* firmly distinguish follicular dendritic cell sarcoma and IPT; the follicular cell type sarcoma has CD21 and CD35 immunoreactive cells and a low percentage of CD68 immunoreactive cells or even lack of inflammatory infiltrate along with morphological nuclear atypia\(^\text{25}\). Radhi *et al.* present an interesting case of a 7-year-old boy

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*Fig. 2. Inflammatory pseudotumor of the cervix (H&E, X200).*

*Fig. 3. Inflammatory pseudotumor of the cervix (SMA, X200).*

*Fig. 4. Inflammatory pseudotumor of the cervix (CD 68, X400).*
with a retroperitoneal tumor mass mimicking IPT on needle biopsy. Surgical resection and histopathology revealed actinomycotic granules with associated suppurrative inflammation. Gomori methenamine silver, although not pathognomonic of actinomycosis, was strongly supportive of the diagnosis.

As early as 1986, Dehner tried to finalize the IPT story concluding that it was a “self-limited polymorphic proliferative lesion whose etiology is unknown”\textsuperscript{27}. However, there are some authors whose experience is contradictory with the pure inflammatory nature of IPT. This mostly relates to its potential for local recurrence, development of multifocal, noncontiguous tumors, infiltrative local growth, vascular invasion, clonal characteristics and malignant transformation\textsuperscript{14}. Interestingly, these examples did not include any uterus IPT.

In addition, cytogenetic analyses revealed rearrangements of the anaplastic lymphoma kinase (ALK) gene and hence an overexpression of ALK protein in inflammatory myofibroblastic tumors, but not in sarcomatoid neoplasms\textsuperscript{14,24,27}. According to these authors, ALK expression confirms the following: first, the distinctive clinicopathologic entity of IPT; second, it defines the etiology by revealing gene fusion at chromosome 2p23 resulting in ALK protein expression; third, it helps in differentiating from sarcomas which are negative for ALK; and fourth, positive expression is associated with favorable prognosis. The investigators believe that at least a subset of IPT is of neoplastic rather than of inflammatory origin\textsuperscript{26-31}.

In terms of purely morphological grounds, the non-neoplastic nature of our case was obvious. Myofibroblastic spindle cells, with mildly polymorphic nuclei and lack of pathological mitotic activity were demonstrated by positive diffuse and intensive staining of cytoplasm with vimentin, SMA and myoglobin. The interfering mononuclear cells included lymphocytes, plasma cells and many histiocytes, which were positive for CD 68. A fine capillary network, hardly seen in H&E samples, emerged after staining with Factor VIII, while Gomori made reticulin fibers visible. Unexplained positivity for S-100 appeared in some spindle cells. Although studies show consistent negativity for S-100, some particularly should be mentioned. Kroupouzos et al. report S-100 positivity in a case of cutaneous Rosai-Dorfman disease, which presented histopathologically as an inflammatory pseudotumor\textsuperscript{23}. Another case of lymph node myofibroblastoma, a lesion with many features in common with IPT, showed positivity of some spindle cells for S-100, which could not be explained by the authors. Ambrosani et al. suggest that both lesions are a peculiar type or a different stage of abnormal lymph node reactivity\textsuperscript{33}. There are also some controversies about cytokeratin expression. Most reports show consistent negativity, but there are some authors who found positive cytokeratin expression in tumor cells appearing as myofibroblastic\textsuperscript{27,34,31}. Swanson et al. describe several cases of overlapping immunohistochemistry of malignant lesions\textsuperscript{36}. Tumor spindle cells were negative to desmin. Interestingly, Trombetta et al. report positive staining of myofibroblasts to vimentin, cytokeratin and desmin in IPT\textsuperscript{34}. In our case IPT showed an absolute lack of cytokeratin and desmin expression. There was no positivity for p53. Reports on p53 expression in IPT are controversial and a uniform conclusion cannot be drawn from available investigations. Still, Hussong et al. confirmed that IPT tumors positive for p53 showed recurrence or malignant transformation\textsuperscript{35}. An interesting study by Ledet et al. compared p53 expression for IPT and sarcoma. All sarcomas were positive for p53 and all IPT cases were consistently negative, even the one that had recurred for several times and another one subsequently dedifferentiated to sarcoma\textsuperscript{38}. Although p53 expression was positive in one of 15 IPT cases, while p53 gene missense mutation was revealed in two cases by polymerase chain reaction (PCR), Yamamoto et al. do not support the theory that p53 plays a major role in the pathogenesis of IPT\textsuperscript{39}.

Therapy consists of surgical resection, which is the most common and so far the best treatment, when it is possible. There is no uniform and unequivocal recommendation in the literature whether and when to use additional therapy. All data concerning adjuvant therapy like corticosteroids, radiotherapy and chemotherapy suggest early, frequent and prolonged vigilance, and in some cases it was successful\textsuperscript{40}. However, additional therapy for IPTs that show a high risk of recurrence indicated by ill-defined margins or intra-abdominal, mesenteric, omental, and retroperitoneal localizations is strongly supported\textsuperscript{41}.

According to some authors, pronounced inflammatory reaction is the main characteristic of IPT. Therefore, the logical option is anti-inflammatory treatment suggested by Hakozaki et al.\textsuperscript{42}. According to Su et al., a trial of NSAID treatment may both confirm the diagnosis of IPT and treat the tumor successfully.

Although extremely rare in the uterus, and especially in the cervix, IPT should be taken in consideration if differential diagnosis of a mesenchymal lesion of the
cervix is questionable, and if another non-neoplastic condition, especially a tumor-like inflammatory and reparative-like lesion, is a matter of differential diagnosis.

It may be said that the course of IPT is characterized by low but not insignificant possibility of malignant behavior including local invasiveness, recurrence or malignant transformation. Therefore, we suggest a palette of immunohistochemical agents with p53 or ALK in addition to standard immunohistochemical procedures. Negative p53 expression or positive ALK expression should be considered as a favorable IPT diagnosis.

According to the studies mentioned above, a lot about IPT needs to be clarified. First and foremost, the statement that IPT is of neoplastic origin according to cytogenetic and PCR results should be undisputedly confirmed in larger series. Flow cytometry, FISH, karyotype analysis and detection of fusion oncogenes should be welcomed, and if possible, become a regular addition to the histopathologic work-up because it could help explain local recurrence or even malignant transformation leading to postoperative complications.

Controversial immunohistochemical findings challenge the pathologist to further investigate IPT and genesis of myofibroblasts. There are still open questions implied by karyotype abnormalities connected with malignant behavior. Were those IPTs malignant since the onset and not recognized as such at the moment of detection or did they just dedifferentiate?

Three years after surgical IPT excision with no histologic evidence of malignancy, and without any adjuvant therapy, our patient is feeling well, with no signs of relapse. In this as well as in other similar cases we suggest long-term follow up.

References


Sažetak

UPALNI PSEUDOTUMOR GRIĆA MATERNICE: PRIKAZ SLUČAJA I PREGLED LITERATURE

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Prikazani slučaj je treći dosad opisani upalni pseudotumor grića maternice. Upalni pseudotumor smatra se dobroćudnom, samoograničavajućom tvorbom nejasne etiologije. Povezuje se s neuobičajenim odgovorom tkiva na ozljedu, prethodnu infekciju ili s autoimunim poremećajem. Iako iznimno rijedak na ovome mjestu, upalni pseudotumor bi se diferencijalno dijagnostički trebao uzeti u obzir ako se radi o mezenhimalnoj tvorbi nalič tumoru ili reparativnoj promjeni. U prosincu 2003. u našu bolnicu je zaprimljena 18-godišnja nulipara zbog disfunkcionalnog krvarenja. Slučajni nalaz pri ginekološkom pregledu bila je solitarna tumorska masa nalič leiomionu, koja je mjerila 4,2 puta 3,8 cm, podrijetlom iz grića maternice. Tumor je kirurški odstranjen. U analizi tumorskih uzoraka primijenjeno su: H&E, Gomori, pankitokreratin, vimentin, SMA, mioglobin, desmin, S-100, CD-68, Faktor VIII i p53. Mikroskopska analiza H&E uzorka pokazala je karakterističnu mezenhimalnu promjenu građenu od vretenastih stanica koje pokazuju morfološke značajke miofibroblasta, fibroblasta i histiocita pomiješanih sa znatnim brojem upalnih stanica. Imunohistokemijska analiza pokazala je pozitivnu reakciju na vimentin, SMA, mioglobin, CD-68, dok su pojedinačne tumorske stanice bile neočekivano pozitivne na S-100. Gomori i Faktor VIII naglasili su retikulinsko-kapilarnu mrežu. Tri godine nakon odstranjenja upalnog pseudotumora bez histoloških naznaka malignosti bolesnica se osjeća dobro i nema recidiva bolesti. U ovom kao i u drugim sličnim slučajevima preporučili bismo dugotrajno praćenje bolesnica.

Ključne riječi: Bolest grića maternice – patologija; Bolest grića maternice - imunohistokemiija; Granulum plazmatskih stanica – patologija;
Prikaz slučaja