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

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Summary

The third recorded case of an inflammatory pseudotumor (IPT) of the cervix is reported.

IPT 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 fungal or bacterial infection and autoimmune disorders.

In December 2003, an 18-year-old nulliparous woman presented in our hospital with dysfunctional bleeding. An incidental finding of a solitary leiomyoma-like mass, measuring 4.2 by 3.8 cm, originating from the cervix, was detected by gynecological examination. The tumor was surgically excised. Samples were stained by H&E, Gomori, pan-cytokeratin, vimentin, SMA, 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 a positive reaction to vimentin, SMA, myoglobin, CD-68, and some tumor cells were unexpectedly positive to s-100. Gomori and Factor VIII emphasized the reticulin/capillary network.

Although extremely rare in this site, IPT should be taken into consideration if mesenchymal lesion or a tumor-like inflammatory and reparative-like lesion is a matter for differential diagnosis.

Surgical resection is the commonest therapy, but corticosteroids, NSAIDs and chemotherapy are also used.

Two years after IPT excision with no histological evidence of malignancy, our patient is feeling well with no signs of relapse. In this as well as in other similar cases we would suggest a long-term follow-up.

KEYWORDS: *cervix, inflammatory pseudotumor, immunohistochemistry, p53*

UPALNI PSEUDOTUMOR VRATA MATERNICE: PRIKAZ SLUČAJA S PREGLEDOM LITERATURE

Sažetak

Prikazujemo treći dosad opisani slučaj upalnog pseudotumora (IPT, od engl. inflammatory pseudotumor) vrata maternice.

IPT se smatra dobroćudnom, samoograničavajućom tvorbom nejasne etiologije. Bolest se povezuje s neuobičajenom reakcijom tkiva na ozljedu, prijašnju gljivičnu ili bakterijsku infekciju i autoimunosne poremećaje.

U prosincu 2003. 18-godišnja žena koja dotad nije rađala došla je u bolnicu radi disfunkcionalnog krvarenja. Na ginekološkom pregledu slučajno je na vratu maternice otkrivena odvojena nakupina slična leiomiomu veličine 4,2 x 3,8 cm. Tumor je kirurški uklonjen. U analizi uzoraka primijenjeni su: hemalaun-eozin (H&E), Gomori, pancitokeratin, vimentin, SMA, mioglobin, desmin, s-100, CD-68, faktor VIII i p53.

Mikroskopska analiza uzoraka bojanih H/E pokazala je distinktivnu mezenhimnu tvorbu građenu od vretenastih stanica s morfološkim značajkama 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 naglašavali su retikulinsko-kapilarnu mrežu.

Iako iznimno rijedak na ovome mjestu, upalni pseudotumor bi se diferencijalno dijagnostički trebao uzeti u obzir ako se radi o mezenhimalnoj tvorbi nalik tumoru ili reparativnoj promjeni. Pored kirurške resekcije koja je najčešći oblik liječenja, u liječenju ove tvorbe također se rabe i kortikosteroidi, nesteroidni protuupalni lijekovi te kemoterapija.

Dvije godine nakon uklanjanja IPT bez histoloških naznaka zloćudne bolesti bolesnica se osjeća dobro i nema recidiva bolesti. U ovom kao i u drugim sličnim slučajevima preporučili bismo dugotrajno praćenje bolesnica.

KLJUČNE RIJEČI: *vrat maternice, upalni pseudotumor, imunohistokemija, p53*

INTRODUCTION

During the past five years more than two hundred cases of inflammatory pseudotumor (IPT) were described. They were mostly localized in the lungs, liver or spleen, not so often in the kidney, bladder, orbit or CNS, 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 epidural space of the thoracic spine (1), ethmoid sinus (2), trigeminal nerve (3), diaphragm(4), but there are IPTs of cutaneous (5), oral (1, 7) or pituitary (8) localizations.

We report on the third recorded case of an inflammatory pseudotumor (IPT) of the cervix (9, 10). Only seven previously described cases deal with IPT in the uterus (9-14).

Recently, it has been recommended to use the term inflammatory myofibroblastic tumor for lesions called inflammatory pseudotumor (IPT), plasma cell granuloma, omental mesenteric myxoid 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 entities (15). The use of the term inflammatory pseudotumor (IPT) is now of historic significance, but it is still the most descriptive.

IPT has become an almost ubiquitous non-neoplastic tumoral condition. It occurs mainly in children and adolescents with a slight female predominance. Approximately 20% of cases are associated with pyrexia, weight loss, elevated ESR and sometimes anemia. Tumor size depends on the site but it is most often in the 5-10 cm range.

There is recent evidence of possible multifocal localization and even congenital recurrence (16).

Curiously enough, overall local recurrence develops in 14% of patients between three months and seven years. IPT 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, respectively (17).

Metastatic disease, recorded in less than 5% of cases, can hardly be predicted on morphological grounds. According to some authors, cases with a clearly atypical cytomorphology can be regarded as malignant (15).

The condition is thought to be related to an unusual tissue response to injury, past fungal or 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 uterus, and symptoms secondary to the presence of the tumor.

PATIENT AND METHODS

In December 2003, an 18-year-old nulliparous woman presented to Dr. Ivo Pedišić General Hospital, with 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 trauma or induced artificial abortion in her history.

An incidental finding of a solitary leiomyoma-like mass, measuring 4.2 by 3.8 cm, originating from the cervix, turned up during gynecological examination. The dimensions measures and site were confirmed by ultrasound.

Surgical extirpation of tumor was achieved while preserving the rest of the uterus. According to the gynecologist who carried out the surgery, the tumor could not be evacuated as easily as ex-

pected. Part of the tumor mass seemed to have infiltrated the posterior wall of the cervix. The majority of the lower cervix was extirpated, accordingly.

The surgical specimen was embedded in paraffin and 5μm sections were stained by standard *H&E* and special histological stain *Gomori*. In order to achieve a definite diagnosis, the material was subsequently analyzed using a special histological technique *Gomori* and a immunohistochemical palette consisting of *pan-cytokeratin, vimentin, smooth muscle actin, myoglobin, desmin, s-100, CD 68, factor VIII* and *p53* .

RESULTS

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, white-yellowish with hemorrhage and necrosis areas. The border between the tumor and healthy cervix was indistinct.

Microscopic evaluation

of a 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, but lymphocytes and neutrophiles could be seen in smaller or larger clusters depending on different HPFs (Fig. 1-3). Some nuclei seemed to be plump and vesicular. The mass lacked a capsule and the border with the scant tissue of the uninvolved portion of cervix was ragged.

Immunohistochemical staining

showed a positive reaction of spindle cells to vimentin, smooth muscle actin, myoglobin and S-100. The inflammatory infiltrate was positive to CD-68 but recognized only histiocytes. The positive expression was analyzed descriptively and

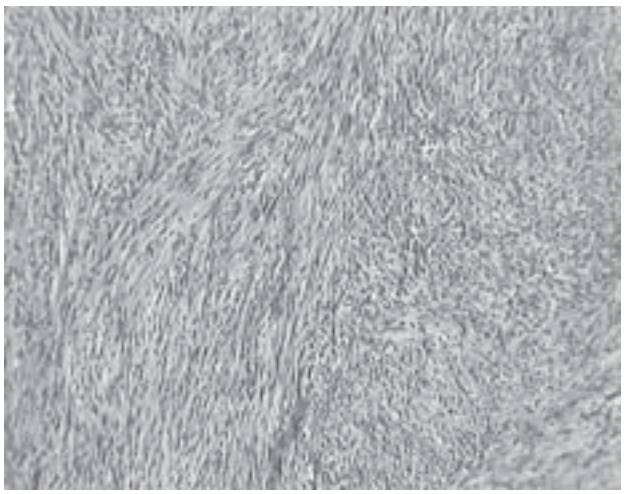

Figure 1. Inflammatory pseudotumor, scanning (H/E)

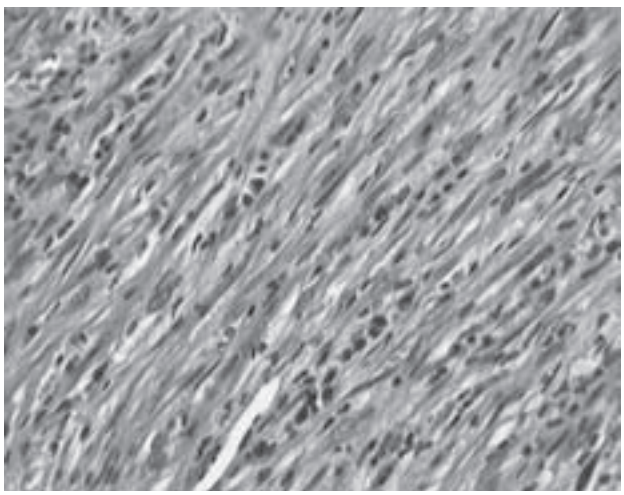

Figure 2. Inflammatory pseudotumor, medium power (H/E)

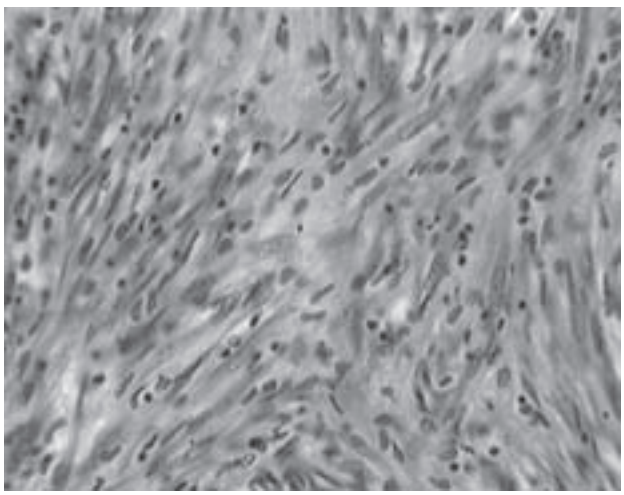

Figure 3. Inflammatory pseudotumor, medium power (H/E)

semiquantitatively. Pan-cytokeratin, desmin, and p53 showed no expression in tumor samples. Factor VIII and Gomori emphasized the capillary IPT network, but tumor cells were negative.

DISCUSSION

IPT was firstly introduced in 1939 by Brunn who described two lung tumors (18). Its modern name which connected and supposed inflammatory etiology and tumorous mass was introduced in 1954 by Umiker and Ivorsen (19). The lungs are the usual location but recently there are increasing number of reports dealing with extrapulmonary sites with liver being commonest 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 and infections conducive to organizing pneumonia, M. avium intracellulare, C. jejuni, B. sphaericus, C. burnetti, EBV, E. coli, occlusive phlebitis of intrahepatic veins) or previous abdominal surgery, trauma, ventriculoperitoneal shunt, radiotherapy, steroid usage, and some genetic factors (20). Most recently Navai et al. described IPT of the testes as a part of an acute retroviral syndrome (21).

According to Arber et al. EBV is detectable in a large number of spindle cells in 66.7% of hepatic and 50% of splenic IPTs (22). Although this case study included only two patients with splenic IPT, further studies confirmed the previous observations (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 (22, 23). As most positive EBV tumors are localized in the liver and spleen, Chan considered them different from the IPT of organs and proposed the term IPT of follicular dendritic cell type (24). But Chan and Fletcher firmly distinguish follicular dendritic cell sarcoma and IPT; the follicular cell type of the former has for first one having CD21 and CD35 immunoreactive cells, and a low percentage of CD68 immunoreactive cells or even lack of inflammatory infiltrate along with morphological nuclear atypia (25).

Radhi J et al. presented an interesting case of a 7-year old boy with a retroperitoneal tumor mass mimicking IPT at needle biopsy. Further surgical resection and pathohistological analysis disclosed actinomycotic granules with associated suppurative inflammation. Gomori methenamine silver, although not pathognomonic of actinomycosis, was strongly supportive of the diagnosis (26).

Already in 1986, Dehner tried to finalize the IPT story concluding that it was a "self-limited polymorphic proliferative lesion whose etiology is unknown" (27). But there are some authors whose experience contradicted 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 transformations (11). Interestingly, these examples did not include any uterus IPTs.

The use of ALK protein in addition to classic IH methods has been suggested, because cytogenetic analyses revealed rearrangements of the anaplastic lymphoma kinase (ALK) gene and hence an overexpression of ALK protein in inflammatory myofibroblastic tumors. Different studies confirm ALK positivity in high percentage of IPT cases, but not in sarcomatoid neoplasms (11, 24, 27). ALK expression according to these authors confirms the following: first, the distinctive clinicopathologic entity of IPT; second, it defines 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, a positive expression is associated with favorable prognosis.

ALK 1 and p80 positivity, chromosomal rearrangements involving 2p23 and abnormalities in flow cytometric DNA analysis support the neoplastic nature of IPT (28). Strong evidence of neoplastic origin was provided in studies analyzing the karyotype of patients with IPT. Su et al. noted the loss of chromosome 6 in two of three cases and a ring chromosome derived from chromosome 8 in the third case. Snyder et al. and Treissman et al. also reported chromosomal translocations in IPT (29). Recently, fusion oncogenes, TPM3-ALK and CLTC-ALK, responsible for *in vivo* transformation of both mesenchymal and lymphoid human cell lineages have been discovered in IPT by Lawrence and Bridge, respectively (30, 31). Both, TPM3-ALK and CLTC-ALK are fusion oncogenes identical to that observed in ALCL. The investigators believe

that at least a subset of IPT is of neoplastic rather than of inflammatory origin.

In recent years, immunohistochemistry has been used vastly in the histological diagnosing of IPT. Immunohistochemical analyses only increase the cost but do not improve the patient's diagnosis, therefore we modestly propose a range of immunohistochemical agents in order to achieve the final diagnosis of IPT .

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 staining with vimentin, SMA and myoglobin. The interfering mononuclear cells included lymphocytes, plasma-cells, and many histiocytes which were positive to 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 to s-100 appeared in some spindle cells. Although studies show consistent negativity to s-100, some particularly should be mentioned. Kroumpouzos et al. reported s-100 positivity in a case of cutaneous Rosai-Dorfman disease which presented histopathologically as an inflammatory pseudotumor (34). Another case of lymph node myofibroblastoma, a lesion with many features in common with IPT, describes positivity of some spindle cells to s-100 which could not be explained by the authors. Ambrosiani et al. suggest that both lesions are a peculiar type or a different stage of abnormal lymph node reactivity (35). There are also some controversies about cytokeratin expression. Most reports show consistent negativity, but there are some authors who have found find out a positive cytokeratin expression in tumor cells appearing as myofibroblastic (27, 36). Overlapping immunohistochemistry of malignant lesions is described in several cases of Swanson's study (37).

Tumor spindle cells were negative to desmin. Interestingly, a study by Trombetta et al. reports positive staining of myofibroblasts to vimentin, cytokeratin and desmin in IPTs (36). In our case IPT showed an absolute lack of expression to cytokeratin and desmin. In addition, there was no positivity to p53. Reports about 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 to p53 showed recurrence or malignant transformations (38). An interesting study by Ledet et al. compared p53 expression for IPTs and sarcomas. All sarcomas were positive to p53 and all IPTs were consistently negative, even one which had recurred for several times and another which dedifferentiated later to sarcoma (39). Although p53 expression was positive in one out of 15 cases of IPT, while p53 gene missense mutation was revealed in two cases by PCR, Yamamoto et al. do not support the theory that the p53 plays the major role in the pathogenesis of IPT (40).

Differential diagnosis may be confusing. Therefore, Gilks et al. simplify it by dividing cases into three groups in terms of the presence of spindle cells (leiomyomas and leiomyosarcomas, benign et malignant fibrous histiocytomas and nodular fasciitis), plasma cells (plasmacytomas) and lymphocytic cells (malignant lymphomas). Granulomatous diseases like Crohn's disease, sarcoidosis and xantogranulomatous tumor-like masses can sometimes blur the main diagnosis. The presence of *E. coli* in a lesion previously diagnosed as IPT was the excluding factor in one case (13). The sarcomatoid variant of anaplastic large cell lymphoma could mimic inflammatory myofibroblastic tumor because of similar histology and cytoplasmic ALK and α-smooth muscle actin expression (41).

Therapy consists of surgical resection which is the commonest and so far the best treatment, if it is possible. There is no uniform and unequivocal recommendation in literature whether to and when to use additional therapy. However, additional therapy for IPTs that show a high risk of recurrence indicated by ill-defined margins or intraabdominal, mesenteric, omental, and retroperitoneal localizations is firmly supported (42).

Heightened inflammatory reaction is the main characteristic of IPT according to some authors. Infection, trauma, previous abdominal surgery, radiotherapy, chemotherapy and steroid use are thought to play a role in IPT genesis (43, 44). For the clinician it is of great significance to know that IPT should be considered in any solid tumor that occurs in association with a chronic inflammatory response. It may also match the differential diagnosis of pulmonary sequestration (43).

Therefore, the logical reaction is anti-inflammatory treatment suggested by Hakozaki et al.

(44). According to Su et al. a trial of NSAID treatment may both confirm the diagnosis of IPT and treat the tumor successfully. The adopted protocol resulted in resolved IPTs in two children aged 6 and 14 years within 2 to 4 months (45). Positive results about NSAID therapy were also reported by Colakoglu et al. who suggested that IPT should be the subject of differential diagnosis of the liver in terms of a possible tumorous process (46).

There are rare cases when corticosteroids were administered, but they are not a common rule. Radiation as well as chemotherapy was successful in case involving malignant IPT localization without the possibility of adequate excision or in a local IPT recurrence (12, 47). Still, it must be noted that recurrence appeared after steroid therapy and radiation in a case of intracranial IPT, but it was successfully treated by cytostatics afterwards (47). All data concerning adjuvant therapy suggest early, frequent and prolonged vigilance (17).

Although extremely rare in the uterus, and especially in the cervix, IPT should be taken into 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 for differential diagnosis.

Hence, the absence of trauma or recent surgery, the absence of Michaelis Guttman bodies, negative special stains for microorganisms together with a distinctive histological appearance of the tumor confirmed by a palette of immunohistochemical agents (Table 1) should facilitate the confirmation of IPT.

According to the previously mentioned data, it might be said that the course of IPT is usually benign and self-limited with a low but not insignificant possibility of malignant behaving including local invasiveness, recurrence or malignant transformations. 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.

Two years after surgical IPT excision with no histological 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 a long-term follow-up.

Modern times need modern technology and, 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 undeniably confirmed in larger series. Flow cytometry, FISH, kariotype analysis and detection of fusion oncogenes should be welcomed, and if possible, be a regular addition to pathohistological procedure, 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 kariotype abnormalities connected with malignant behavior. Were those IPTs malignant since onset and not recognized as such at the moment of their discovery or did they just dedifferentiate?

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