Mesenchymal tumors of the uterine corpus with heterologous and hematopoietic components: A study of ten cases and review of the literature

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Summary

Objective: To study the histopathological features of mesenchymal tumors of the uterine corpus with heterologous and hematopoietic components, and review their histogenesis and differential diagnosis from other neoplastic and non-neoplastic lesions.

Methods: Ten cases of mesenchymal tumors of the uterine corpus, massively infiltrated by hematopoioetic cells, or composed of other benign heterologous elements (adipose tissue in the present cases) were retrieved from the archival files of our laboratory and studied histopathologically. Immunohistochemistry was applied in selected cases.

Results: Six of our studied cases were diagnosed as leiomyomas, two as lipoleiomyomas, one as a symplastic lipoleiomyoma, and one as an endometrial stromal tumor. The leiomyomas were massively infiltrated by lymphocytes (5 cases) or eosinophils (one case). Immunohistochemical study of the leiomyomas with massive lymphocytic infiltration revealed the presence of a predominantly B-cell population within the infiltrate, which was polyclonal in nature. The endometrial stromal tumor was severely infiltrated by histiocytes, and was positive for vimentin, CD10, PgR and negative for actin, desmin, ER and caldesmon.

Conclusion: The presence of hematopoietic or heterologous elements within an otherwise bland uterine leiomyoma or endometrial stromal tumor may give rise to diagnostic difficulties. Regularity of the tumor margins, low mitotic activity and absence of nuclear atypia or necrosis should be established for the exclusion of a malignancy. In the presence of massive lymphocytic infiltration of a leiomyoma the clonality of the infiltrate may aid in differentiating it from a malignant lymphoma. The pathogenesis and clinical significance of these rare neoplasms remain to be clarified.

Key words: Mesenchymal; Endometrial stromal tumors; Leiomyomas; Lipoleiomyomas; Hematopoioetic; Infiltration.

Introduction

According to the World Health Organization (WHO, 2003) classification of tumors of the female genital organs, mesenchymal neoplasms of the uterine corpus are defined as tumors derived from the mesenchyme of the corpus consisting of endometrial stroma, smooth muscle and blood vessels or admixtures of these, and comprise endometrial stromal and related tumors, smooth muscle tumors and other mesenchymal tumors (such as mixed endometrial and smooth muscle tumor, perivascular epithelioid cell tumor and adenomatoid tumor) [1].

The commonest mesenchymal tumors of the uterus are leiomyomas, with an overall incidence of 4-11%, and an incidence of 40% in women over the age of 50 years [2]. Obstruction of the uterus, interference with pregnancy, and abscess formation are the major complications of leiomyomas [2]. Transformation into leiomyosarcoma is also possible and is indicated by rapid growth, hemorrhage and necrosis in the leiomyoma [3]. The distinction between a benign and a malignant smooth muscle tumor is usually not a difficult task for an experienced pathologist because of the typical macroscopic and microscopic features of leiomyomas [4]. However, problems in the differential diagnosis from other, benign or malignant, lesions may be encountered during the pathologic evaluation of a leiomyoma when the tumor is accompanied by certain degenerative changes, placed under the term "leiomyoma variants" [2, 4]. These variants include the massive presence of hematopoioetic cells within the leiomyoma as well as the presence of other benign heterologous elements such as fat, osseons, skeletal muscle or cartilage [5, 6].

Endometrial stromal tumors are histogenetically related to smooth muscle tumors since they both originate from the primitive uterine mesenchyme [2]. Their histogenetic relationship is obvious in non-neoplastic uterine lesions exhibiting smooth muscle metaplasia of the endometrial stroma, or in cases of mesenchymal tumors displaying features of both endometrial stromal and smooth muscle differentiation [2, 7, 8]. These heterologous tumors are considered as endometrial stromal neoplasms when the smooth muscle component is limited in less than one third of the tumor mass and the stromal features are prominent, and are referred to as combined smooth muscle-stromal tumors when the smooth muscle component is sizable [2]. Infiltration of endometrial stromal tumors by hematopoietic components has also been reported and may give rise to diagnostic difficulties [5, 6, 9].

In our study we present ten cases of mesenchymal tumors composed of hetereologous elements or infiltrated by hematopoietic compoments, and discuss their particular clinicopathological features, with emphasis on the differential diagnosis.

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Materials and Methods

After reviewing the archival files of our laboratory for the last five years (from 2000 to 2004) we retrieved ten cases of mesenchymal tumors with hematopoietic or heterologous elements in a total of 379 surgical specimens of hysterectomies or myomectomies. Patient age ranged from 18 to 76 years old (with a mean of 46.7 years). Four patients were submitted to total abdominal hysterectomy with oophorectomy, one to total abdominal hysterectomy without oophorectomy, and the remaining to simple removal of the tumor (myomectomy). The patients' postoperative course was uneventful and they are all alive and well so far (with the follow-up period varying from one to five years).

In all cases paraffin-embedded tissue was available and additional sections were obtained for the application of a streptavidin-biotin immunohistochemical study. The primary antibodies used in this study were: desmin (D-R-11), LCA-CD45 (LCA 88), B-cell-CD20, T-cell-CD45RO (UCHL-1), K-l chain (K53) and L-l chain (HP-6054), vimentin (VIM 3B4), CD10 (56C6) and h-caldesmon (h-CD).

Results

The histological diagnoses of the ten reviewed cases were: leiomyoma (6 cases), lipoleiomyoma (2 cases), symplastic lipoleiomyoma (1 case) and endometrial stomal tumor (1 case).

All leiomyomas presented grossly as firm white well circumscribed nodules, without areas of softening or hemorrhage. One leiomyoma in particular had a microcystic appearance on cut section and larger cystic spaces filled with dense myxomatous material. Microscopic examination of these six tumors showed the typical features of leiomyomas: interlacing bundles of spindle-shaped smooth muscle cells without cytologic atypia, mitotic activity or necrosis.

In five leiomyomas severe infiltration of the tumor by a polymorphous cellular population was observed. The infiltration consisted mainly of mature small lymphocytes and, to a lesser degree, of lymphoblasts, plasma cells and histiocytes, and was confined to the tumor without extending to the myometrium or the adjacent endometrium. According to the results of the immunohistochemical analysis, lymphocytic infiltration was composed almost exclusively of B-cells and rare T-cells. Immmunohistochemistry was also positive for desmin, LCA, and, kappa and lamda light chains, suggesting the presence of a polyclonal B-cell population.

The sixth leiomyoma was a giant tumor occurring in a young 18-year-old woman and measuring 16 cm in the greatest diameter. At microscopic examination the tumor was massively infiltrated by eosinophils. Areas of muxomatous degeneration were also observed. The clinical history and the results of additional laboratory tests excluded the presence of a peripheral blood eosinophilia as well as the possibility of any allergic or parasitic disease.

The two lipoleiomyomas appeared grossly as large white tumors, measuring 5 and 8 cm in the greatest diameter, with soft yellow foci or streaks on cut section. Microscopically these tumors contained smooth muscle cells intermingling with mature adipose tissue.

The symplastic lipoleiomyoma was an otherwise typical leiomyoma on macroscopic examination, measuring 5.5 cm in the greatest diameter, with yellow greasy areas on cut section. Microscopic examination revealed the presence of normal and multinucleated giant smooth muscle cells. Mitotic activity was relatively rare (less than 5 MF per 10 HPF). A striking amount of fat was also present, but the adipose tissue did not share the atypia of the smooth muscle component of the tumor.

The endometrial stromal tumor appeared grossly as a well circumscribed yellowish nodule of firm consistency, measuring 7.5 cm in the greatest diameter. Microscopic examination of the tumor showed a lesion consisting of uniform, small cells with rare mitotic activity and absence of cytologic atypia or necrosis,which was massively infiltrated by histiocytes. There was no indication of vascular or lymphatic permeation. The lesion margins were focally irregular, but did not invade the myometrium. Immunohistochemistry was positive for vimentin, CD10, PgR and negative for actin, desmin, ER and caldesmon. The final diagnosis was endometrial stromal tumor of low malignant potential.

Discussion

Leiomyoma variants are detectable in approximately 65% of uterine leiomyomas [2]. They are considered as the result of secondary changes of leiomyomas, which include, among others, hyaline degeneration, mucoid or myxomatous degeneration, calcification, cystic changes, fatty metamorphosis, hydropic degeneration and infiltration by hematopoietic components (lymphocytes, eosinophils, histiocytes) [2]. Even though the presence of these degenerative changes does not seem to have any impact on prognosis or therapy, their recognition is important in order to avoid diagnostic confusion with other inflammatory, reactive or neoplastic lesions [4, 10, 11].

Massive lymphocytic infiltration of leiomyomas is a rare pathologic finding, whose pathogenesis and clinical significance have not yet been fully elucidated [12]. Inflammation, use of an intrauterine device (IUD), preoperative treatment with gonadotropin-releasing hormone (GnRH) analogs, abnormal immune compliance, a specific human HLA alteration or a viral infection of the tumor have all been suggested by various authors as possible causative agents of this process [10, 13, 14-17]. The histological findings of this rare neoplasm consist of the typical spindle-celled lesion of leiomyomas, infiltrated by a heterologous cellular population made up of small lymphocytes, immunoblasts, and plasma cells, with or without formation of germinal centers [3, 11]. This pattern may be confused with hematopoietic disorders such as malignant lymphoma, small lymphocytic lymphoma, or even Hodgkin's disease [2, 18]. Differential diagnoses from these lesions must be based both on macroscopic and microscopic findings. A firm, well circumscribed tumor without areas of softening or hemorrhage is most likely benign [11, 13]. In addition, the presence of a polymorphous cellular population consisting of

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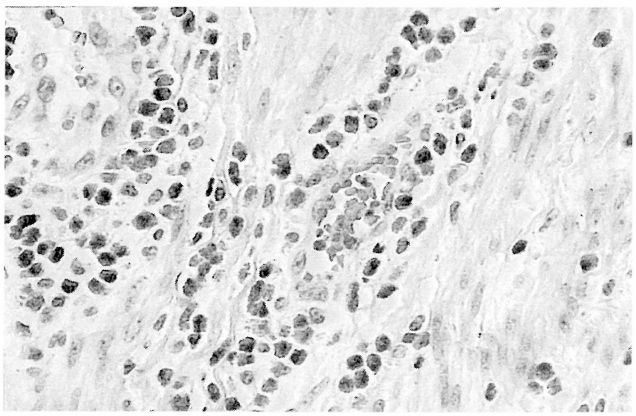
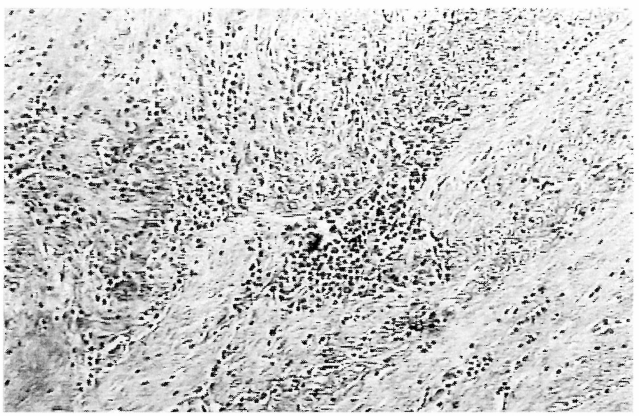


Fig. 2



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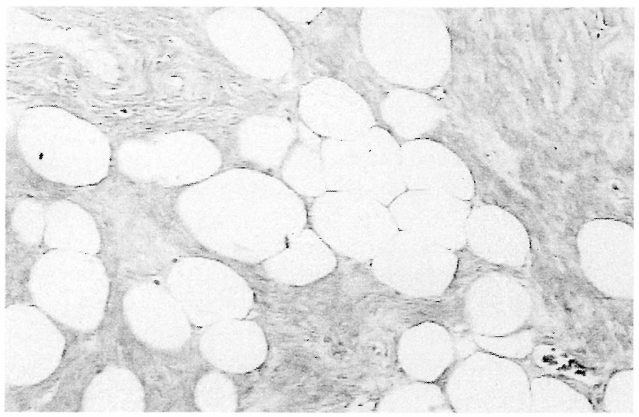

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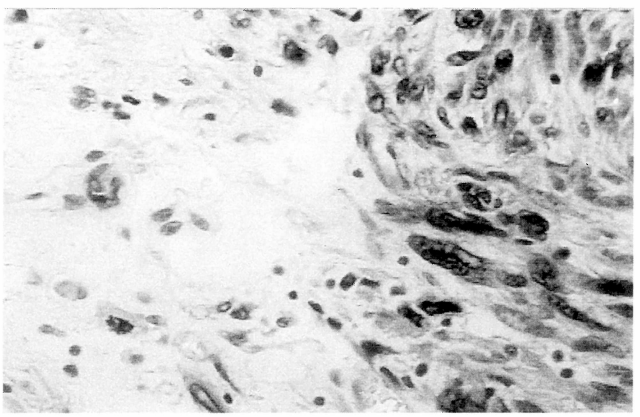

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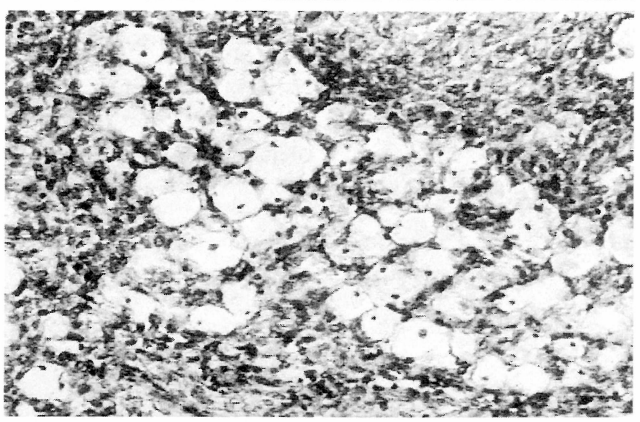

Figure 1. — Histological section of a leiomyoma with extensive eosinophilic infiltration (hematoxylin-eosin x 250).

Figure 2. — Histological section of leiomyoma with lymphocytic infiltration (hematoxylin-eosin x 100).

Figure 3. — Histological section of a lipoleiomyoma (hematoxylin-eosin x 250).

Figure 4. — Histological section of a symplastic lipoleiomyoma (hematoxylin-eosin x 250).

Figure 5. — Histological section of stromal tumor with remarkable infiltration of histiocytes (hematoxylin-eosin x 250).

normal hematopoietic cells without large lymphoid cells (predominating in malignant lymphoma) or Reed-Sternberg cells (present in Hodgkin's disease) is typical of a leiomyoma with massive lympocytic infiltration [2, 18, 19]. The latter should also be differentiated from pyomyoma or inflammatory pseudotumors [3, 20, 21]. Pyomyoma is a term referring to leiomyomas with cystic degeneration and suppuration [3]. These tumors were more common in the first half of the past century, with their incidence being practically diminished since the advent of antibiotics [3]. Inflammatory pseudotumors grossly simulate leiomyomas, and are differentiated from them on the basis of histology alone [20, 21]. The presence of neutrophils is clear evidence of an acute inflammatory process, excluding the diagnosis of leiomyoma with massive lymphocytic infiltration in favor of the inflammatory pseudotumor [21]. In our five studied cases of leiomyomas with massive lymphocytic infiltration the diagnosis was based on the polymorphous character of the cellular population and the confinement of the lesion to the tumor. The clinical records of the patients (including laboratory testing for hematological and autoimmune diseases) did not reveal any of the thus far proposed causative factors that we mentioned previously.

Most previous studies of leiomyomas with massive lymphoid infiltration indicate a preponderance of T cells within the infiltrate [12, 19]. On the contrary, most primary and secondary lymphomas of the uterus are shown to be of the diffuse large B-cell type [12]. Therefore, the clonality of the infiltrate may aid in excluding the diagnosis of malignant lymphoma in cases with diagnostic difficulties, and especially when the lymphocytes

are predominantly of the B-cell type. In a recent study regarding a uterine leiomyoma with lymphoid infiltration, molecular analysis showed a mixed population of B and T lymphoid cells, whose B-cell counterpart was monoclonal in nature [12]. According to the authors of this report, a clonal infiltrate may be "typical of leiomyoma nodules infiltrated with lymphocytes, the antigenic environment of the leiomyoma nodule being the triggering stimuli" [12]. In our study, we failed to demonstrate a clonal lymphocyte infiltrate, as immunohistochemical analysis of our five cases was suggestive of a predominantly B-cell population which was polyclonal in nature.

Only three cases of uterine leiomyomas with eosinophils have been previously reported to our knowledge [22]. Eosinophilic infiltration of leiomyomas is considered as a "variation" of lymphocytic infiltration and an extremely rare histological finding of limited clinical significance [2]. According to a previous report, the presence of eosinophils in leiomyomas could be attributed to tissue injury and reflect a response consisting of wound healing, tissue remodeling and fibrosis [22]. In our studied case of a giant leiomyoma massively infiltrated by eosinophils the presence of these hematopoietic cells could not be clinically or pathologically explained. However, both blood and tissue eosinophilia have been previously described in association with uterine leiomyosarcoma, a fact indicating the need for extreme caution in the evaluation of uterine smooth muscle neoplasms with severe eosinophilic infiltration [23].

Lipoleiomyomas of the uterus are benign, heterologous mesenchymal tumors consisting of mature spindle cells, connective tissue and mature lipocytes [24-26]. They are extremely rare neoplasms even though a limited amount of fat may be commonly found in otherwise typical leiomyomas [6]. The origin of lipoleiomyomas is not yet clarified although various pathogenetic mechanisms have been proposed for the interpretation of the formation, such as lipomatous degeneration of leiomyomas, metaplasia of smooth muscle cells or even a real neoplastic process [27]. The differential diagnosis should include the much rarer lipomas and liposarcomas [4]. According to certain authors, lipoleiomyomas should also be differentiated from leiomyomas with fatty degeneration on the basis of the presence of mature adipocytes [4]. Leiomyomas with fatty degeneration contain lipids instead of mature adipose tissue [4]. Nonetheless, other authors evade such a distinction [2]. Symplastic leiomyomas are smooth muscle tumors with atypical cells which may be multinucleated or carry enlarged hyperchromatic nuclei [28, 29]. The differentiation from leiomyosarcomas is mainly based on the absence of coagulative tumor cell necrosis and the presence of relatively low mitotic activity (less than 5 MF/10 HPF) [4, 6]. The distinction between these two separate clinical entities may be challenging, especially in the absence of high mitotic activity, as leiomyosarcomas may contain areas without increased mitotic activity [6]. Our case of a symplastic leiomyoma was also characterized by the presence of a striking amount of adipose tissue. We believe that the term "symplastic lipoleiomyoma" would be the most appropriate for such a neoplasm, even though it could also be designated as an atypical lipoleiomyoma. Atypical lipoleiomyomas have been previously reported [30-32]. The biological behavior of "atypical" or "symplastic" leiomyomas cannot be safely predicted, and they are generally considered as of uncertain malignant potential [6, 33, 34]. In our case, the benign nature of the neoplasm could be partly confirmed by the absence of any patient relapse so far (for the last five years following the operation).

Endometrial stromal tumors may be easily confused with highly cellular leiomyomas because of their similar morphology (densely cellular tumors composed of cells from round to spindle-shaped with little cytoplasm) [6]. Their distinction often requires the application of immunohistochemistry which is typically negative for EMA, H-caldesmon, and desmin, and positive for vimentin and CD10 in the presence of an endometrial stromal tumor, while most highly cellular leiomyomas are CD10 negative and actin, desmin, EMA and h-caldesmon positive [2]. Regularity of the tumor margins and absence of mitotic activity, necrosis and myometrial or vascular invasion are also essential in excluding a diagnosis of endometrial stromal sarcoma [35].

One of our studied cases was a neoplasm exhibiting both morphologically and immunohistochemically [vimentin (+), desmin (-), CD10 (+), caldesmon (-)] the features of an endometrial stromal neoplasm with rare mitotic activity, absence of necrosis and extensive histiocytic infiltration. The designation as of low malignant potential was based on the focal irregularity of its margins and its low mitotic activity. Mesencymal uterine tumors may, on rare occasions, exhibit histiocytic infiltration [9]. The histiocytes may be diffusely scattered in the tumor, as in our case, or located within artetrial walls suggesting the presence of vasculitis [10]. In a recent report, histiocyte density was found to be significantly higher in uterine leiomyomas than in the adjacent normal myometrium, a finding suggestive, according to the authors, of a possible pathogenetic role of histiocytes in neoplastic proliferation of uterine smooth muscle [36]. We can only hypothesize that histiocytes might play a similar role in the pathogenesis of endometrial stromal nodules, given the histogenetic relationship of the endometrial stroma and smooth muscle. However, the presence of histiocytes in uterine mesenchymal neoplasms seems to be clinically insignificant [10]. The main issue of concern is therefore the proper recognition of the histiocytes by the pathologist and the avoidance of their probable confusion with neoplastic cells. Immunoreactivity for the marker CD68 may efficiently aid in the differential diagnosis, as histiocytes typically express CD68, while neoplastic cells do not [37].

Conclusions

Although the majority of uterine leiomyomas are easily diagnosed pathologically, diagnostic difficulties may arise in the presence of various heterologous elements within the leiomyoma. Massive infiltration of leiomyomas or other benign mesencymal tumors such as

endometrial stromal nodules by hematopoioetic cells is an interesting yet rather unexplored phenomenon whose pathogenesis and clinical significance remain to be clarified. The presence of adipose tissue in a leiomyoma, especially when accompanied by atypia of the smooth muscle component of the neoplasm, is a rare finding, and should be differentiated from the much rarer lipomas and liposarcomas. Regularity of the tumor margins, low mitotic activity and absence of nuclear atypia or tumor necrosis should be established in all conspicuous mesenchymal neoplasms for the exclusion of malignancy. In the presence of massive lymphocytic infiltration of a leiomyoma the clonality of the infiltrate could aid in differentiating it from a malignant lymphoma, although monoclonal B-cell lymphocytes may occasionally infiltrate totally benign smooth muscle neoplasms. In the case of an "atypical" or "symplastic" lipoleiomyoma, close postoperative follow-up is recommended because the biological behavior of these tumors remains uncertain.

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