

MAFFUCCI'S SYNDROME: REPORT OF A CASE AND REVIEW OF THE LITERATURE

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Enchondromatosis is a nonhereditary skeletal disorder, characterized by the persistence of cartilage in several bones that are formed by enchondral ossification. In 1900, Ollier described a condition that resembled the osseous component of the syndrome that Maffucci had described 19 years earlier. In Maffucci's syndrome (MS), the enchondromas coexist with cutaneous and sometimes visceral hemangiomas. Fewer than 200 cases of Maffucci's syndrome have been published in the English literature.

Malignant transformation of the skeletal lesions is a common feature of MS, and has been observed in approximately 30% of reported cases, with chondrosarcomas being the most common.¹ The development of various types of neoplasms is a well-known complication of MS, and is recognized as a principal factor affecting prognosis. In 1948, Kuzma and King² first reported an ovarian mesenchymal tumor associated with MS, and since then, sporadic reports have referred to ovarian tumors of sex-cord stromal derivation in patients with enchondromatosis.³⁻¹³ We describe the first case of bilateral ovarian serous cystadenomas and polycystic ovarian disease in a patient with MS, and review previously reported gynecologic pathology seen in association with enchondromatosis.

Case Report

A 19-year-old single woman known to have Maffucci's syndrome, with a three-year history of right flank pain, was referred to our institution for evaluation and management of a pelvic abdominal mass that was suspected of being a juvenile granulosa cell tumor. Menarche occurred at the age of 15 years, and no menstrual disturbances were noted. The family history revealed that no other family member was affected. Deformities and multiple enchondromas were more conspicuous in the left hemiskeleton than in the right. A subcutaneous soft tissue mass in the left arm was

diagnosed in early infancy, and had been removed when the patient was six years old. Subsequently, she underwent above-elbow amputation of the left arm for a large disfiguring mass eight months prior to her current presentation. The surgery had been performed at another hospital, and the histology of this mass was not available for review. She had a history of excision of two other subcutaneous hemangiomas.

Laboratory data showed hemoglobin of 10.29 g/dL (normal value, 12.09-16.0 g/dL), with microcytic and hypochromic anemia. Selected tumor markers, including estradiol concentration 164 pmol/L (normal value, 48-903 pmol/L), human chorionic gonadotropin <2.0 IU/L (0.00-10.00 IU/L), and alpha fetoprotein 3.7 µg/L (0.00-10.00 µg/L), were within normal limits. Radiologic examination, including CT scan and MRI of abdomen, showed a multilocular cystic mass extending above the umbilicus. The spleen and abdominal wall showed vascular malformations. Chest scan showed a hemangioma in the lung less than 1 cm in diameter. Exploratory laparotomy showed bilateral ovarian masses without ascites. Left salpingo-oophorectomy and wedge resection of the right ovary were performed. There was no evidence of intra-abdominal spread. Postoperative recovery was uneventful, and the patient was discharged and given an appointment for follow-up.

Pathology

Tissue available for pathologic examination included the left ovarian cystic mass with attached fallopian tube, and two wedge biopsy specimens from the right ovary. The left ovarian cyst was 20 cm in maximal dimension. It was unilocular and the internal surface was smooth gray and lacked any solid or papillary growth. The fallopian tube was stretched over the cyst but was otherwise normal. The two wedge resections from the right ovary measured 4.5 cm and 3.5 cm in maximal dimension. The cut surface revealed multiple cysts ranging in size from barely visible to 1.0 cm in maximal dimension. The intervening tissue was whitish and solid.

Microscopic examination of the left ovary showed ovarian tissue containing numerous primordial follicles and some cystic follicles (Figure 1). Multiple atretic follicles were identified but no corpora lutea or albicantia were seen.

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Accepted for publication 31 March 2000. Received 23 November 1999.



FIGURE 1. Left ovary with two follicular cysts (H&E, 40x).



FIGURE 2. Wall of the cyst from left ovary showing ciliated single epithelial cell lining (H&E, 100x).



FIGURE 3. Right ovary with two follicular cysts and part of the wall of the serous cystadenoma (H&E, 40x).



FIGURE 4. Right ovary with prominent vascular pattern of the stroma (H&E, 100x).

The ovarian stroma showed foci of prominent smooth muscle proliferation, and the ovarian cortex was very thick and fibrous. The large cyst was lined by a single layer of cuboidal-to-low columnar ciliated epithelial cells (Figure 2). There was no evidence of any stratification or nuclear atypia. The underlying stroma was dense and fibrous. The two wedge resections from the right ovary showed numerous cystic follicles lined by granulosa cells and having an outer thicker layer of luteinized theca interna cells (Figure 3). The right ovary showed a multilocular cystic lesion, with a lining of a single layer of cuboidal-to-low columnar ciliated epithelial cells. The ovarian stroma showed areas of hyperthecosis, edema and prominent irregular vascular spaces (Figure 4). Few inclusion cysts were seen, with some showing tubal metaplasia. No corpora lutea or albicantia were identified. The diagnosis of synchronous bilateral ovarian serous cystadenomas and polycystic ovarian disease was made.

Discussion

Ollier's disease (OD) is a rare nonhereditary congenital syndrome characterized by multiple enchondromas. When the latter are associated with multiple hemangiomas, the designation Maffucci's syndrome (MS) is used. The emergence of several neoplasms is a well-known complication of both these diseases, and is recognized as a principal factor affecting patient prognosis. Although chondrosarcoma is by far the most common sarcoma seen in MS,¹ a wide variety of non-cartilaginous tumors have been reported. Some enchondromas have been reported to develop into osteosarcoma or dedifferentiated chondrosarcoma.¹⁴⁻¹⁸

One of the earliest studies was conducted by Lewis and Ketchum.⁴ In their extensive review of the world literature of 105 cases of patients who had MS, they found that 15% of them developed chondrosarcoma. Among the various

neoplasms which they described, five were gynecologic, two were described as malignant mesenchymal ovarian tumors, one was ovarian thecoma, one was uterine polyp, and another one was uterine fibroid.

In their tri-institutional retrospective study with long-term follow-up, Schwartz et al.¹⁹ identified 44 patients with multiple enchondromas. One patient developed an ovarian granulosa cell tumor. They found no evidence of hereditary transmission or of a familial tendency to this syndrome. In addition, they compared the risk of development of malignant neoplasms in patients with MS and those with OD.

The risk of the development of a skeletal or non-skeletal malignant neoplasm for patients with MS is probably close to 100% if they are followed for a long enough period. The risk of the development of a malignant neoplasm in patients with OD is considerably less. In 1993, Kaplan et al.²⁰ reviewed 65 cases of MS. They found that 37% had a malignant lesion, and chondrosarcoma occurred in 30%. There were four cases of ovarian tumors, three mesenchymal (one juvenile granulosa cell tumor, one fibrosarcoma and one adenosarcoma), and one was an adenofibroma. They also found that the number of non-mesodermal tumors was high at 30% (14/49), contrary to the usual belief that MS is mainly a mesodermal dysplasia.

Because the ovarian neoplasm most commonly documented in association with enchondromatosis is juvenile granulosa cell tumor (JGCT), our case was referred with a strong suspicion of this diagnosis. At least 14 cases of JGCT have been reported in association with enchondromatosis, four associated with MS, and the rest with OD.²⁻¹³ The accumulation of cases developing ovarian JGCT indicates that this neoplasm appears to be the next most frequent tumor occurring in patients with enchondromatosis. The clinical and morphological features of the tumors and their behavior have not differed significantly from those of JGCTs occurring in patients without these syndromes.¹² Single examples of ovarian fibroma²¹ and fibrosarcoma²² have also been reported in patients with MS. The patient with the fibrosarcoma, who was 17 years old, was re-explored 18 months after left oophorectomy, and there was no evidence of metastatic tumor.

Polycystic ovarian disease has not been previously described in association with MS. Although our patient did not have clinical manifestations of polycystic ovarian disease, it is possible that this was the primary pathology, and the development of bilateral epithelial neoplasms was a secondary phenomenon. This idea was considered by Resta et al.,²³ who found that hyperplastic and metaplastic changes of the ovarian surface epithelium and related inclusion cysts can be regarded as morphologic precursors of common epithelial tumors of ovary. The finding of inclusion cysts and tubal metaplasia in the right ovary of our case may support this hypothesis. The right ovary in our patient showed a prominent stromal vascular pattern,

which may be related to the generalized hemangiomas seen in MS, noting that our patient had both subcutaneous and visceral hemangiomas. It is not clear whether the ovarian pathology seen in our case was only coincidental or whether it could be attributed to a common embryonic meso-ectodermal developmental dysplasia.^{16,24} This concept is supported by reports of dysplastic conditions seen in association with enchondromatosis, such as bilateral renal agenesis,²⁵ and the congenital anomalies indicative of Goldenhar's syndrome (oculoauriculovertebral dysplasia).²⁶

Because of the common tendency for development of neoplasms in patients with enchondromatosis, it is important that these patients are followed carefully, with special emphasis on periodic imaging of abdomen and pelvis for occult neoplasms. Additional studies are needed to understand the pattern of transmission and the proposed embryonic meso-ectodermal developmental dysplasia of enchondromatosis.

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