



Fig. 1. Photomicrograph of the endocervical biopsy showing microglandular hyperplasia. (Hematoxylin and eosin. Original magnification $\times 200$.)

of low cuboidal cells. Their nuclei were darkly stained but were small and uniform. No mitotic figures were seen. The stroma contained many cells with acute and chronic inflammation (Fig. 1). No endometrial tissue was present in the endometrial biopsy. The cervical biopsy was not remarkable. Microscopic slides of the initially resected cervical lesion were reviewed and revealed a polypoid lesion with the same histologic appearance as that seen in the endocervical biopsy. No carcinoma was present. Our final pathologic diagnosis was microglandular hyperplasia of the endocervix most likely secondary to the long-term estrogen treatment.

Premarin was discontinued, and no further treatment was given. She has been followed at the outpatient clinic for six months and has had no evidence of cervical disease or vaginal bleeding. A repeat biopsy four months after the first biopsy showed chronic endocervicitis but no evidence of hyperplasia.

It is known that long-term use of estrogen sometimes produces hyperplasia of the endometrial glands. On the other hand, effects of estrogen on the endocervical epithelium are relatively unknown. The histologic appearance of the cervical lesion in this case is similar to that of microglandular hyperplasia of the cervix seen in women using oral contraceptive hormones. This change has also been observed, though less frequently, in the cervixes of pregnant women and those who have received exogenous progestogens and is considered secondary to progestogens.^{1, 2} Since this patient had no exogenous progestogens, the lesion is most likely secondary to estrogen she had received for the last 11 years.

Microglandular hyperplasia of the cervix frequently manifests itself as polypoid or nodular excrescences and microscopically is composed of closely arranged small glands, sometimes with a reticular pattern. These glands are characteristically lined by flattened or cuboidal cells instead of tall columnar cells seen in a normal endocervix. Their nuclei may be hyperchromat-

ic but are small and uniform. Mitotic figures are usually absent. Although it is biologically and histologically benign, the lesion occasionally has been mistaken for adenocarcinoma on account of its unusual histologic appearance.¹ In the present case, the older age of the patient, as well as the absence of a history of exogenous progestogens, may have been another factor in the initial erroneous diagnosis.

REFERENCES

1. Candy and Abell, M. R.: Progestogen-induced adenomatous hyperplasia of the uterine cervix, *J. A. M. A.* **203**: 323, 1968.
2. Nichols, T. M., and Fidler, H. K.: Microglandular hyperplasia in cervical cone biopsies taken for suspicious and positive cytology, *Am. J. Clin. Pathol.* **56**: 424, 1971.

Anosmia and hypogonadism associated with elevated luteinizing hormone levels and multiple congenital anomalies

JEROME H. CHECK, M.D.

ABRAHAM E. RAKOFF, M.D., F.A.C.O.G.

ALVIN F. GOLDFARB, M.D., F.A.C.O.G.

PHILIP SLIPYAN, M.D.

Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, Thomas Jefferson University School of Medicine, Philadelphia, Pennsylvania

ANOSMIA AND hypogonadotropic hypogonadism of hypothalamic origin have a well-known association.

Reprint requests: Dr. Jerome H. Check, Thomas Jefferson University Hospital, 1025 Walnut St., Room 300, Philadelphia, Pennsylvania 19107.

Table I. Results following the first administration of GnRH

LH (mI.U./ml.)	Minutes	FSH (mI.U./ml.)
48	0	7
400	30	16
330	60	17.5
29	90	17.5
20.8	120	17

Table II. Results following the second administration of GnRH

LH (mI.U./ml.)	Minutes	FSH (mI.U./ml.)
39	0	13
71	30	23
53	60	24
34	120	23

Bardin and colleagues have suggested, in addition, an unexplained lack of response of the testes to exogenous gonadotropins. There is a report of a 58-year-old man with anosmia, hypogonadism, and elevated gonadotropins.¹ We present here a woman with anosmia and elevated luteinizing hormone (LH) levels but normal follicle-stimulating hormone (FSH) levels and many congenital anomalies.

The patient, a 21-year-old woman with congenital anosmia and polydactyly and syndactyly, experienced menarche at age 15. She had 10 spontaneous menstrual periods, and the last menstrual period was eight months previously. She had a history of congenital glycosuria (12.9 Gm. per 24 hours), but excretion of other phenylketones, amino acids levels, and glucose tolerance were normal. The longest interval between menstrual periods was one year. Thelarche and pubarche occurred at age 12, and sexual development was normal. The skin was normal, with no acne, hirsutism or oiliness.

At age 17, she had withdrawal periods induced with Provera, but Provera treatment failed six months previously. Basal body temperature charts were anovulatory.

The family history was negative for anosmia or hypogonadism. One brother had insulin-requiring juvenile diabetes. The mother denied drug ingestion during pregnancy.

Physical examination showed the patient to be 64½ inches tall and eunuchoid with an arm span of 70 inches. She weighed 134½ pounds. She had a broad flat nose with an almost cleft palate. There were multiple congenital anomalies of both hands and feet including syndactyly, brachydactyly, absence of digits, malrotation, and extra phalanges. Vertical and horizontal nystagmus was noted. There was poor vision in the right eye with defects in the nasal inferior and temporal superior fields. Anosmia was present. The secondary sexual development was normal, and pelvic examination was within normal limits.

Laboratory studies revealed a normal complete blood count, electrolyte levels, 12 parameter Sequential Multiple Analyzer test, electrocardiogram, and chest roentgenogram. Despite glycosuria, the six-hour glucose tolerance test was perfectly normal. Twenty-four urinary protein excretion was

54 mg.; 17-ketosteroid levels were slightly increased at 18 mg. per 24 hours; the serum testosterone value was at the upper limit of normal at 95 µg per cent; serum FSH was normal at 7 mI.U. per milliliter while LH was increased at 48 mI.U. per milliliter. Serum estrogens were low, at 0.2 mg. per milliliter; urinary estrogens determined one year previously were slightly low at 4 mg. per 24 hours. These estrogen values correlated with the hormonal vaginal smear which showed a small amount of intermediate proliferation, indicating a mild estrogen deficiency.

The skull roentgenogram and tomograms of the sella turcica were normal. The electroencephalogram showed a Grade III photoparoxysmal response, a dysrhythmia that can be associated with a clinical convulsive disorder in 50 per cent of cases.

A gonadotropin-releasing hormone (GnRH) stimulation test, in which a bolus of 100 µg of GnRH was given intravenously, was carried out, and the results are shown in Table I.

With the elevated base-line LH, low normal FSH, slightly elevated 17-ketosteroids, and upper normal testosterone, we thought the patient might have polycystic ovaries despite the clinical absence of hirsutism, acne, or palpably enlarged ovaries. A laparoscopy was performed, and both ovaries appeared slightly smaller than normal and in a resting stage. The left ovary was slightly nodular. No corpus lutea were seen. Biopsy revealed bilateral capsular fibrosis with several unstimulated primary follicles and a few early stimulated follicles.

The patient failed to respond to 100 mg. of Clomid for five days. Human menopausal gonadotropins (Pergonal) were then given intramuscularly, in a dose of 150 U. daily. After three days, there was no improvement in the vaginal smear, cervical mucus was absent, and the plasma estrogens were 0.3 mg. per milliliter. However, after three more days of Pergonal stimulation, the cervical mucus became abundant, clear, and acellular with excellent spinnbarkeit, and the vaginal smear showed a good estrogenic effect, consisting of 60 per cent superficial and 40 per cent large intermediate proliferation. Plasma estrogen increased to 1.0 mg. per milliliter.

Following stimulation with Pergonal, the patient had three spontaneous menstrual periods over a four-month period of time. A repeat GnRH stimulation test was performed, and the results are shown in Table II. It should be noted that prior to the second GnRH test the patient had a moderate estrogenic effect on the vaginal smear.

This is the first reported case of anosmia, secondary amenorrhea with estrogen deficiency, and elevated LH. In the case of the 58-year-old man with hypergonadotropic hypogonadism, there were some questions as to whether the anosmia was a chance occurrence since the testicular biopsy was similar to that seen in Klinefelter's syndrome.

It is interesting that the ovarian biopsy with the thickened capsule and unstimulated primary follicles resembled the case of gonadotropin-resistant ovaries in association with secondary amenorrhea reported by Kim.²

A hypothalamic defect in this case is suggested by the associated central defects of anosmia, broad flattened nose, almost cleft palate, vertical and horizontal nystagmus, visual field defects, and electroencephalogram abnormalities. In further support of the diagnosis of a

hypothalamic defect were the supranormal LH response on GnRH testing and the failure of FSH to return to base-line values two hours after injection, and also the failure of Clomid response.

The gonadotropin-resistant nature of the ovaries was suggested by the presence of only unstimulated primary follicles despite elevated LH. This is further supported by the poor response to 450 I.U. of human menopausal gonadotropins. This resistance would be mild in comparison to the typical cases of gonadotropin-resistant ovaries in view of the excellent response to 900 I.U. of Pergonal. In contrast to typical gonadotropin-resistant ovaries, where FSH is usually higher than LH, here the LH was increased while the FSH was low normal. This raises the possibility of an associated pituitary defect with anosmia also affecting FSH to a greater degree than LH, although other hypotheses could alternatively explain these results.

We are not aware of any known syndrome encompassing anosmia, oligomenorrhea, central defects, anomalies of hands, feet, and face, and congenital glycosuria.

REFERENCES

1. Males, J. L., and Schneider, R. A.: Hypergonadotropic hypogonadism with anosmia, *Acta Endocrinol.* **71**: 7, 1972.
2. Kim, M. H.: "Gonadotropin-resistant ovaries" syndrome in association with secondary amenorrhea, *Am. J. Obstet. Gynecol.* **120**: 257, 1974.

Uterine leiomyoma with hemangiopericytomatous foci: Histogenetic implications

LOUIS H. HONORÉ, F.R.C.P. (C.)

*Department of Pathology, Vancouver General Hospital,
Vancouver, British Columbia, Canada*

DESPITE THE FREQUENCY of occurrence of uterine leiomyoma, its histogenesis remains unsettled. Meyer's¹ suggestion that its cell of origin is the myometrial smooth muscle cell is widely accepted, but the alternate hypothesis,² implicating the vascular pericyte as the mother cell of both uterine leiomyoma and hemangiopericytoma, is gathering more support.³ The present report of the finding of a uterine leiomyoma with hemangiopericytomatous foci offers further support for the "vascular" origin of this tumor.

A 28-year-old patient presented with dyspareunia from a painful vaginal scar, resulting from an old rectovaginal fistula. At operation, the scar was excised, and the uterus was found to contain multiple leiomyomas, one of which was shelled out. This tumor, measuring 5 by 5 by 4 cm., had the typical gross

and histologic features of a leiomyoma with negligible mitotic activity and nuclear pleomorphism. In two blocks, multiple discrete, well-circumscribed, unencapsulated foci of hemangiopericytomatous change were seen. These foci consisted of small, rounded or elongated masses of tightly packed ovoid to spindle cells with indistinct cell borders, scanty cytoplasm, and a dusky ovoid nucleus exhibiting minimal mitotic activity. In addition, there were a few thick-walled capillaries with barely detectable lumina, smothered by overlapping ovoid cells with a striking concentricity (Fig. 1). The reticulin stain was diagnostic, showing the proliferating cells to lie outside the capillary basement membrane and to be embedded in a pericellular reticulin framework (Fig. 2).

This case demonstrates unequivocal association of leiomyoma and hemangiopericytoma. The possibility of a collision tumor, i.e., a hemangiopericytoma invading a leiomyoma, can be excluded by the presence of discrete microfoci of the hemangiopericytoma located exclusively in the center of the leiomyoma (as shown by multiple sections), by the absence of interstitial spread of the hemangiopericytoma causing distortion or pressure atrophy of the adjacent smooth muscle cells, and finally by the imperceptible grading of the two lesions. As a result, the hypothesis is advanced that this tumor arises from a single cell type with the potentiality of differentiating into pericyte or smooth muscle. On the basis of experimental studies, the most likely cell type is the undifferentiated adventitial fibroblast.⁴

This hypothesis is further supported by three independent lines of evidence—morphologic, biochemical, and "paraendocrine." The morphologic evidence rests on the close interrelationship between endothelium, pericyte, and smooth muscle, which has been shown to exist during adult angiogenesis⁵ and during the development of certain vascular tumors.⁶ The biochemical evidence is supplied by a recent study of the molecular constitution of the collagen extracted from uterine leiomyomas.⁷ The collagen was shown to have the $[\alpha_1(III)]_2$ constitution typical of fetal tissues, gut, and blood vessels.⁸ This piece of evidence favoring a vascular origin of leiomyomas is more direct but, before it can be accepted as final, additional studies on the collagen composition of leiomyomas and other soft tissue tumors will be required. The "paraendocrine" evidence depends on the production of erythropoietin by uterine leiomyomas. Many tumors have been reported to be associated clinically with erythrocytosis, but only two extrarenal tumors actually have been shown to produce erythropoietin, i.e., the cerebellar hemangioblastoma and the uterine leiomyoma.⁹ While this coincidence may have no biological significance, it may also indicate a more basic similarity between these two tumors. The cerebellar hemangioblastoma recently has been shown by ultrastructural and organ culture studies¹⁰ to consist of multiple cell lines, including a significant pericytic component. Therefore, it is possible that this common ability of the cerebellar hemangioblastoma and uterine leiomyoma to secrete erythropoietin reflects their origin from a similar primitive

Reprint requests: Dr. Louis H. Honoré, Department of Pathology, Grace General Hospital, 241 LeMarchant Rd., St. John's, Newfoundland, Canada, A1E 1P9.