A CASE OF STEIN-LEVENTHAL SYNDROME

by

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A clinical entity arising out of an endocrine gland is best established if the symptoms and signs are correlated with specific anatomic features and functional changes in the affected organ. Such a correlation has not been found to exist in cases of Stein-Leventhal syndrome, especially those associated with hirsutism. During the past thirty-two years, there has been much speculation and controversy as to the aetiology the site of pathological changes and the nature of hormonal imbalance in a typical case of Stein-Leventhal syndrome. Stein and Leventhal in 1935, first described a group of cases with bilaterally enlarged, pale, smooth, polycystic ovaries with thickened capsules, with symptoms of infertility, oliogomenorrhoea, and sometimes hirsutism and obesity. They expressed their conception of what has now become known as the "Stein-Leventhal Syndrome".

Case Report

Mrs. F. B., aged 25, para 0 + 0, married for 15 years, was first seen in gynaecological out-patients' department of the Nilratan Sircar Medical College & Hospital on November 11, 1967, with complaints of irregular menstrual bleeding for one and half months and a history of primary infertility and hirsutism for the last ten years. Menstrual history revealed—menarche was at the age of 12 years; for the first five years the periods were regular and normal. But from the age of 17 years, she began to miss periods for two to three months at a time followed by a heavy flow with passage of clots but without any pain, and each period lasting for about ten to thirty days or, at times, even more prolonged. L.M.P. was on 27th September 1967, which continued as irregular bleeding for 45 days, i.e. till the day of her admission. For the last ten years, she noticed growth of hair on the face, over the upper lip, over the arms, legs and thighs and abdomen. There was no acne or change in the voice.

Obstetric history—married at age of 10 years, para 0 + 0.

Other past history—nothing significant.

Physical examination revealed—a tall (5′ 3″), healthy (weight—57 Kg.) woman with a heterosexual facial hirsutism. There was male distribution of hair over the upper lip (Fig. 1), abdomen, extremities and axillae. Pubic hairs were exuberant. The breasts were well developed. She was moderately anaemic (Hb.—7.5 gm.%). Pulse—88/min., B.P.—120/70 mm. of Hg. Other systems—no abnormality detected. Local examination did not show any enlargement of the clitoris, and the vulva and vagina were normal. Cervix—was tubular with nulliparous os and healthy. Fornices—both ovaries were palpable but the size could not be made out properly due to much abdominal wall fat and non-co-operation of the patient. Bleeding per vaginam was present.

Special Investigations—(1) Blood—Total W.B.C.'s.—7,200/c.mm. Hb.%—7.5 Gm.% (Hellige), Poly.—76%, lympho.—22%,

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eosino.—2%. Blood sugar—105 mgm.%, Urea—24 mgm.%, N.P.N.—25 mgm.%, Cholesterol—166 mgm.%.

(2) Urine

(3) Stool

No abnormality detected.

(4) Examination under anaesthesia and diagnostic curettage were done on 13-11-67 —revealed uterus—A.V., A.F., slightly bulky (length by uterine sound—3½″). Fornices—both ovaries palpably enlarged; cervix—healthy and tubular.

Curettings—sent for histo-pathological examination.

Report—Late proliferative endometrium seen. No picture of malignancy noted.

(5) Gynaecography—by pushing air into the peritoneal cavity through the abdominal wall—was undertaken on 18-11-67. It showed the characteristic picture of moderate enlargement of both ovaries. The uterus was of normal size (Fig. 2.).

(6) Peri-renal pneumo-roentgenography —on 2-12-67 showed that both adrenals were normal.

(7) Sex Chromatin study—Sex chromatin positive. No chromosomal studies were undertaken.

(8) Laparotomy — on 14-12-67 — both ovaries were found to be enlarged (3″ x 1½″ x 3/4″)—Three times that of a normal ovary. Each ovary had a smooth, pearly white, shiny capsule. Multiple, small-sized, fluid-filled cysts were found beneath the thick capsule which did not bulge on the surface. The characteristic scarring and indentations of the normal ovaries were absent. The uterus was found to be slightly bulky (corresponding to about 6 weeks, pregnancy size). Both tubes were little longer (4½″ length).

Bilateral wedge resection of both ovaries was resorted to and the tissues were sent for pathological examination. Clips were removed on the 6th post-operative day. Union was good. The patient had to be kept for seven more days in the hospital due to a recurrence of bleeding per vaginam (which had stopped following the curettage) and which was subsequently controlled by neo-progestogen therapy.

Histo-pathological Report — Section shows a fibrous tissue mass with few blood vessels. No Graffian follicle or corpus luteum seen. There is proliferation of theca interna cells. But theca externa are proliferated more than theca interna. (Fig. 3).

Discussion

Though the incidence of typical Stein-Leventhal syndrome is very low (1.4%, Johansson, 1957 and 1.6%, Blewett, 1961), yet the aetiology of the condition has received a great deal of attention and several theories have been postulated to explain it. The aetiology still remains obscure. Since both ovaries are equally involved, it appears that the original stimulus comes from outside the ovary. Stein and Leventhal (1935) suggested that it was due to abnormal stimulation of the ovaries by pituitary hormones. The hormonal imbalance by pituitary dysfunction has been supported by several authors (e.g., Bailey, 1959, Ingersol & McDerrnott, 1950). Uptil now there is no report in the literature of the histological study of the anterior pituitary gland in a patient with the classical Stein-Leventhal syndrome. From the hormonal standpoint there is a great diversity of opinion among different authors. Bailey (1959) thought the syndrome was due to deficiency of the follicle stimulating hormone (F.S.H.), but Ingersol *et al* (1950) showed a continuous and erratic elevated excretion of the luteinising hormone (L.H.) in the urine of patients with Stein-Leventhal syndrome, as compared to the single ovulatory peak in normally menstruating women. There has also been much speculation as to whether morphological and hormonal changes leading to Stein-Leventhal syndrome occur in the ovary or

in the adrenal gland or in both. But, both adrenal biopsy and 17-ketosteroids in urine estimated by Leventhal in 1962 showed no abnormality in the suprarenal glands. Unfortunately, no hormonal studies, as well as no biopsy of adrenal glands, have been carried out in the present case, though the perirenal pneumo-roentgenography did not reveal any abnormality in the size of the adrenales.

Recent workers, e.g., Short and London (1961), have found that the ovaries of Stein-Leventhal syndrome have enhanced the ability to produce weakly androgenic steroids, i.e., androstenedione, as compared to normal ovaries. They have demonstrated abnormally high concentrations of this hormone (35 times more concentrated than testosterone) in the cyst fluid in the ovaries of these patients. This substance is present in small amounts in normal ovaries as an intermediate product in the synthesis of oestradiol—17$^{\mu}$ from progesterone. According to Short and London (1961), this increase in androstenedione might be the cause of hirsutism in Stein-Leventhal syndrome. Short (1962) has suggested that the main defect in the ovaries is presumably of the 19-hydroxylase enzyme system by which androstenedione cannot be converted into 19-hydroxy-androstenedione and subsequently to oestrone and oestradiol. This defect, in turn, might be due to some sex-chromosomal anomalies (De Gronchy *et al,* 1961). No detailed chromosomal studies had been done in this case, so no definite opinion can be given.

Regarding the clinical features—hirsutism, infertility (either primary or secondary), and abnormal menstrual history, mainly oligomenorrhagia and secondary amenorrhoea, are usually complained of. Here, the patient complained of menorrhagia preceded by a period of amenorrhoea, as is usually obtained in cases of functional uterine haemorrhage. In a small percentage of cases of Stein-Leventhal syndrome this feature might be present. The history of hirsutism and primary infertility were also present in this case. Obesity is no more a common feature in this syndrome (Stein, 1958) as it was thought to be previously, and the present patient was not obese.

As to the pathological diagnosis, macroscopically the ovaries are usually enlarged, 3-4 times the normal size, with a smooth surface, and a shiny capsule, pearly white in colour. The cut section reveals a thick, fibrous capsule surrounding a stroma containing multiple small cysts filled with clear fluid. Microscopically, the cystic follicles may or may not have layers of granulosa cells. One of the most significant and consistent finding is a hyperplasia of the theca interna cells with frequent luteinizations. The sections are characteristically marked by absence of corpora lutea or corpus luteum cysts. In our case, there were no Graffian follicles, no corpora lutea or corpus luteum cysts. But the hyperplasia of the theca interna though present, was not as evident as suggested by Leventhal. There was no luteinization of theca interna in this case. But here, the theca externa was much more hyperplastic,

as has been found by Roberts and Haines (1960).

The endometrium in Stein-Leventhal syndrome shows a picture of early or mid-proliferative phase. In this case, the picture was of late proliferative one, the endometrial biopsy being taken on the 47th day of continuous bleeding preceded by 60 days of amenorrhoea. Not until recently, emphasis has been laid on the relationship between the Stein-Leventhal syndrome and the development of endometrial carcinoma as a late complication (as has been shown by Speert (1949), Jackson and Dockerty (1957), etc. Though the symptoms of menstrual aberrations and hirsutism continued for a prolonged period of 8-10 years, yet there was no development of endometrial carcinoma in this patient.

Bilateral wedge-resection of the ovaries is supposed to be the ideal treatment in these cases and the same treatment had been adopted in this case. Stein (1958) showed that 95% of patients with Stein-Leventhal syndrome had been cured of oligomenorrhoea and amenorrhoea and 88.7% became pregnant following bilateral wedge-resection of the ovaries. Recently, some authors have advocated the use of clomiphene citrate and human chorionic gonadotrophins (HCG) in these cases in order to induce ovulation and have obtained encouraging results in some cases.

It may be concluded by saying that it is important always to keep this syndrome in mind when one is dealing with any menstrual abnormality in women with infertility, where obesity may not be present, and hirsutism may be present in only 50% of cases.

Summary

A case of Stein-Leventhal syndrome has been reported along with review of the literature, stress being laid on its importance as a clinical and pathological entity.

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Figs on Art Paper IV