ARRHENOMABLASTOMA OF OVARY

A Case Report with brief review of Literature

by

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The clinical behaviour of dysontogenic tumours of the ovary has always aroused considerable interest, especially where there is an associated hormonal effect. Arrhenoblastoma is a biologically active neoplasm which causes defeminization and virilization of a previously normal female. Attention was first directed to this tumour in 1905, when Pick described a curious testicular-like tumour in an otherwise normal parous female. He called it "Adenoma tubularae testicularae ovarii", and presumed that it arose from an ovotestis. In 1915, Blair-Bell (1915) demonstrated the first functioning tumour. While Meyer (1930) was the first to describe the histologic characteristics and correlated them to its functional effects, and named it "Andreiblastoma", which was later modified to "Arrhenoblastoma". Since then comprehensive reviews and summaries have periodically appeared in the literature. In 1938, Novak reported a series of 51 cases. In 1951, Henderson reported 78 cases, and Javert and Finn, 122 cases. In 1953, Hughesdon and Fraser reviewed the reported cases and accepted 132 as genuine. Upto 1960, Pedowitz and O'Brien could collect 240 cases. In 1965, Novak and Long reviewed all authentic cases of arrhenoblastoma collected from the Ovarian Tumour Registry. Since then sporadic reports have been appearing in the literature. To our knowledge, about 320 cases have so far been reported in the world literature. From India only four cases have been reported so far (Paranjape, 1959; Parekh and Parekh, 1963; Ipye and Mukerjee, 1966, and Banerjee, 1967). Rarity of this condition warrants report of the following case:

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Case Report

Smt. J., 25 years old married hindu female, was admitted in the Medical wards of Medical College Hospital, Jabalpur, on 16-10-1968, with pain followed by distension of the abdomen, and loss of appetite of two months' duration. She had primary amenorrhoea and had not conceived. On general examination, she was grossly emaciated and anaemic. She had hair over the face. The axillary hair were absent, and the pubic hair were sparse and of feminine distribution. Breasts were atrophic and the clitoris was hypertrophic.

The examination of the respiratory

system revealed signs of bilateral pleural effusion. The abdomen was grossly distended, and dilated veins were present over the abdomen. Liver and spleen were not palpable, and ascites was present. Pelvic examination revealed hypoplastic uterus and cervix, and the fornices were free. Rest of the systems were clinically normal.

Investigations: (i) Blood;—Hb., 8.2 gm%., total W.B.C. count 10,320/cu. mm., differential W.B.C. count: P. 71, L 24, E 4, M. 1%. E.S.R., 12 mm/I hr.

(b) Urine analysis revealed no abnormality.

(c) **Liver function tests:** Total proteins, 5.75 gm: albumin, 3.84 gm%, globulin 7.90 gm%. Serum bilirubin less than 0.5 mg%. Van den Bergh, negative. Icteric index, 5 units.

(d) **X-ray chest:** Done on 19-10-1968, showed pleurisy with effusion left side, with shifting of the mediastinum to the right side. Repeated on 26-10-1968, it showed elevation of both domes of diaphragm and haziness of both costo-phrenic angles, suggesting raised intra-abdominal pressure, and bilateral pleural effusion. (Fig. 1).

(e) **Ascitic fluid:** Diagnostic aspiration done on 19-10-1968, yielded blood-stained fluid. Its total protein content was 3.5 gms%, with plenty of R.B.Cs.

(f) **Pleural fluid:** Paracentesis was done on 25-10-1968, and yielded fluid having total proteins 3.0 gms%, with plenty of R.B.C.s.

On 29-10-1968, she experienced difficulty in lifting the left hand. Vaginal examination on 30-10-1968 revealed a hypertrophied clitoris and nodule in the left fornix There was slight bleeding per vaginam. She went into acute respiratory distress and expired on 31-10-1968 at 11 a.m. The autopsy findings were as under:

Gross; Peritoneal fluid was haemorrhagic. There was pleural effusion on both the sides. The heart weighed 120 gms and did not show any specific change. Right lung weighed 150.00 gms. and left weighed 120 gms. and both were collapsed. Liver weighed 720 gms., and was normal on gross examination. Both kidneys weighed 180 gms. and were normal on naked eye examination. The uterus was hypoplastic, and both the tubes were normal. The left ovary was of normal size. Right ovary was replaced by a tumour, 7" x 6" x 5", weighing 1 lb. It was yellowish, friable, and haemorrhagic.

Microscopic; Lungs were collapsed and showed patchy consolidation. Liver, spleen, and kidneys did not show any specific change. Adrenals showed autolytic changes. Endometrium showed proliferative change. Myometrium was normal. Left ovary contained distended graafian follicles. The right ovarian tumour was an arrhenoblastoma of diffuse variety. (Fig. 2).

Comments

Arrhenoblastoma is characteristically a tumour of young women, with maximum incidence in the third decade. However, cases below the age of 10 years have also been reported in the literature. Pedowitz and O'Brien reported 4 cases below the age of 9 years, while O'Hern and Neubecker (1962) observed one case at 9 years. Likewise, Novak and Long (1965) came across three cases below the age of 9 years. Cases at the other extreme of age are reported by Novak and Long (1965) at ages of 64, 67 and 70 years.

There may be a long latent period between the onset of symptoms, and the diagnosis of the tumour, because the earlier symptoms may be minimal, and virilization is a slow process. Moreover, some of the tumours may be non-functioning. The functioning tumours cause de-feminization followed by masculinization. De-feminization is evidenced by oligomenorrhoea followed by amenorrhoea, atrophy of breasts, sterility, and loss of female contour. This precedes signs of virilization, viz. hirsutism, voice changes, and clitorial enlargement. Amenorrhoea is due to the effect of androgens secreted by the tumour, inhibiting the hypo-

physis and suppressing ovarian functions, rather than its effect on endometrium (Meloni, 1955). A tumour may secrete androgens and still may not produce virilization, while some signs of virilization may be marked, and others may be completely absent (Mariuzzi, 1957). Menstrual abnormallities are present in 70-80% of cases, and hirsutism in 60-80% cases. In the present case primary amenorrhoea, atrophy of breasts, hirsutism, and enlargement of clitoris were present.

Although, one commonly expects and does find an atrophic endometrium in these cases, the presence of hyperplastic endometrium does not rule out an androgenic tumour. The paradoxical findings of virilization, menorrhagia and endometrial hyperplasia is explained by the fact that the ovulatory hormone of the pituitary is more sensitive to circulating androgens than the follicular stimulating hormone. Thus, while ovulation is suppressed, follicular stimulation continues, and causes oestrogen production and endometrial hyperplasia (Usizima, 1957). In the present case, though primary amenorrhoea was present, the endometrium was proliferative, indicating some production of oestrogen by the ovary, though insufficient for causing menstruation. Probably, the circulating androgens might be opposing oestrogen.

17-ketosteroid (17-KS) excretion in these cases is usually normal (Speed, 1953), because androgenic substances not excreted as 17-ketosteroids are produced by the tumour. 17-KS is raised only in 1/3 of the cases. Even when 17-KS levels in the urine may be normal, the ratio between androsterone and aetiochonelone may prove useful. Chromatographic studies in these cases may show an increase of only one fraction-androsterone (Pesonen and Mikkonen, 1958).

Chromosomal studies in these cases help to differentiate these cases from those of testicular feminization. Both are indistinguishable histologically. However, the former is chromatin-positive (Fathalla and Kerr, 1966).

In 95% of cases the tumour is unilateral and in 5% cases they are bilateral (Whelton and Christian, (1966). The tumours may vary in size from 2-3 cms. to 25 cms. About 1/6 of the tumours are less than 6 cms. in diameter. Hertz's case weighed 26 lbs. (Novak and Long, 1965). Four cases reported by Kreines and Esselborn (1963) were cystic, and weighed more than 1950 gms. The largest weighed 2790 gms. There is no correlation between the size of the tumour and endocrine activity. Tumours are usually solid, with smooth, lobulated cortex, frequently containing yellowish, greyish, or orange tissue. Haemorrhagic and cystic changes may occur. Cystic tumours are likely to be mistaken for Stein-Leventhal syndrome (Feda *et al.*, 1961).

Meyer (1930) classified these tumours into three histological varieties: (i) well differentiated tubular adenoma, (ii) intermediate form, and (iii) undifferentiated type. Most undifferentiated tumours are most virilizing, while well differentiated ones are least functioning, but Morris and Scully (1958) feel that there is no correlation between the cellular differentiation and endocrine activity. The undifferentiated ones

have to be differentiated from granulosa-theca tumour, and sarcoma. Sandberg (1962) rightly suggests the doctrine that the endocrine effect should be the criterion for classifying the functioning tumours.

The histogensis of these tumours is reviewed in detail by Hertig and Gore (1952) and Hughesdon and Fraser (1953). Meyer (1931) postulated that they arose from undifferentiated male directed 'cell rests' in rete ovarii. Kanter and Klawans (1940) postulate a teratomatous origin for these tumours. Teilum (1949) believes that they arise from a testicular blastoma (androblastoma) in the ovary in which de-differentiation of Sertoli and/or Leydig cells occur. Werner *et al.* (1960) believe that they arise from the 'reserve cells' of the ovary which are capable of dividing. Testicular adenomas, resembling arrhenoblastomas histologically, were experimentally produced in rodents by McKay *et al.* (1960), but they were feminizing in their hormonal effects.

Cases of arrhenoblastoma with pregnancy have been reported by Pedowitz and O'Brien (1960), 10 cases, Novak and Long (1965), 2 cases, Brentnll, and Paula Xavier, one case each. It is possible that these tumours were probably inert at the time of conception, or the androgen secreted did not inhibit ovulation (Pedowitz and O'Brien, 1960). During pregnancy, they either remain inert or become biologically active; in that case they may cause pseudo-hermaphroditism in the infant (if they are active during the first trimester). The female infant may have an enlarged clitoris. During pregnancy, they have to be histologically distinguished from Sternberg's luteoma of pregnancy.

Malignancy in these tumours is found in 22-34% cases. Javert and Finn (1951), 22%; Pedowitz and O'Brien (1960), 21.3%; and Novak and Long (1965) 34%. Microscopic appearances of individual cell pattern is of no help in assessing the malignant propensities in these cases (Novak and Long, 1965). The presence of cell atypia, mitosis, and histologic evidence of infiltration are poor indices of prognosis (Gilvernet and Camps Cordone, 1959).

Treatment

This can be considered under three headings:—

(a) Conservative surgery:—Unilateral salpingo-oophorectomy, or rarely, simple resection of the tumour. It is the treatment of choice in young individuals in whom preservation of childbearing is desirable, when the tumour is encapsulated, unilateral, and without evidence of metastases and ascites.

(b) Radical surgery:—For tumours which are non-capsulated and which show evidence of metastases, regardless of the age of the patient.

(c) Incomplete surgery:—as biopsy, partial excision. They are useful only for making a histological diagnosis of the tumour.

Post-operative deep X-ray is not warranted in well capsulated tumours.

Perhaps, the most dramatic results of the excision of arrhenoblastoma is the reversal of masculinization. In most cases the menstruation returns in 1-3 months. The virilization takes longer to disappear, or may not disappear at all. There may be complete

disappearance of hirsutism, with normal growth of axillary and pubic hair of normal female pattern. Facial hair, and acne disappear, and there is refeminization of body configuration. In a few months there is reappearance of normal female habitus and enlargement of breasts, but hoarseness of voice and enlargement of clitoris may persist.

Pregnancy is recorded after the removal of the tumour (O'Hern and Neubecker-3 cases, Novak and Long-9 cases, Parekh and Parekh, and Banerjee, one case each).

Urinary 17-ketosteroids, if raised, come back to normal after operation. Reappearance of virilism is an indication of recurrence (Meixner, 1958), but sometimes the recurring tumour may be inert (Schultze, 1952). In the present case the diagnosis was confirmed at autopsy.

The 5-year cure rate in malignant cases varies from 14-27%. (Pedowitz and O'Brien, 1960). While the 5 year survival in 90 cases of low malignancy in Novak and Long's (1965) series was 66%.

It is suggested that in arrhenoblastoma cases certain investigations should be carried out before treatment. Several determinations of 17-ketosteroid excretions should be carried out, because of daily variations. Chromatographic studies, intra-venous pyelography, and retroperitoneal pneumography should be carried out to rule out adrenal neoplasms. X-ray of sella turcica should be done to rule out pituitary enlargement. Endometrial biopsy and vaginal cytology should be carried out to assess ovarian functions. While culdoscopy and pneumo-gynography will help in visualising small ovarian neoplasms. Nuclear-sex determinations will differentiate testicular feminization. And therapeutic trials with cortisone will reverse the effects of adrenal cortical hyperplasia. Lastly, laparotomy should be carried out to confirm the diagnosis and execute proper treatment.

Summary

1. A case of arrhenoblastoma with primary amenorrhoea is presented.

2. Aetiological factors, clinical features, pathology, histogenesis, diagnosis and treatment of the condition are briefly discussed and reviewed.

3. A plan of investigation for these cases is suggested.

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See Figs. on Art Paper VIII