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Megalomastia: histological, histochemical and immunohistochemical study

O.Th. Anastassiades[1], T. Choreftaki[1], J. Ioannovich[1], J. Gogas[2], and C.S. Papadimitriou[3]

[1] Department of Pathology, General Hospital of Athens, Messogion 154, Athens 11527, Greece
[2] Second Department of Surgery, University of Athens, Athens, Greece
[3] Department of Pathology, University of Thessaloniki, Thessaloniki, Greece

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Summary. Megalomastia is a rare entity characterized by an uncommon enlargement of both breasts. Unilateral megalomastia is extremely rare. The purpose of this study was to collect information concerning the history of patients with this condition and to investigate its histology in order to outline the profile of this peculiar entity. Fifty cases of megalomastia were studied. In 41 data concerning the history of the patients was complete; there were 32 juvenile, 7 gravid and 2 adult type cases. All three unilateral megalomastias were in the juvenile group. A family history of megalomastia was frequently present; gravid megalomastia was more closely connected with a maternal familial history. A case of simultaneous megalomastia in monozygotic twins is included. The final size achieved by the breasts was independent of the type of megalomastia, the rapidity of breast development and the body weight of the patients. It was greater in breasts containing abundant adipose tissue and less in fibrous breasts. In all cases of megalomastia associated with pregnancy the breasts had lost the ability to produce milk. The main histological feature in all cases was severe damage and destruction of the lobular units associated with extensive fibrosis. In some breasts of all three types of megalomastia ramified new ducts named "juvenile units" had developed and had proceeded to atrophy. Immunohistochemistry revealed that the epithelium of these units was negative for oestrogen and positive to progesterone receptors. A biphasic pathological appearance, consisting of atrophic lobular units and "juvenile units", is diagnostic of megalomastia.

Key words: Megalomastia – Lobular destruction – Immunohistochemistry

Introduction

Megalomastia, also called macromastia or gigantomastia, is a rare condition characterized by an uncommon enlargement of the breasts. It usually affects both breasts and is only rarely unilater (D'Alessandro and Taylor 1986). It appears during puberty and adolescence (Bauer et al. 1987; Durston 1670; Fisher and Smith 1971; Hollingworth and Archer 1973; Sagot et al. 1990; Samuelov and Siplovich 1988), less frequently during pregnancy (Bhattacharaya 1983; Lafreniere et al. 1984; Lewison and Trimble 1960; Luschin-Ebengreuth and Scharnagl 1989; Tchabo and Stay 1989) and exceptionally in adult life (Gavrilescu et al. 1977; Haagensen 1986; Strombeck 1964). The aetiology and the pathogenesis of the condition are obscure, and information concerning the histology, histochemistry and immunohistochemistry is deficient, contradictory or absent. Data mostly refer to the clinical aspects of the syndrome and to the best surgical treatment (De Castro 1977; Furnas 1982; Greeley et al. 1965; Miller and Becker 1979; Ship 1986; Staub et al. 1989; Strombeck 1964). We decided to focus our interest on the histology of the condition using histochemical and immunohistochemical techniques and also to collect as much information as possible regarding the history of the patients.

Materials and methods

The study was based on surgical material derived from 50 cases of reduction mammoplasty made in the Plastic Surgery Unit of the General Hospital of Athens. Surgical material from each breast was fixed in 10% neutral formalin for 24 h after weighing. Pieces of tissue from 15 cases were kept frozen at −70° C.

In cross-sectioning the specimens were composed of solid and fatty tissue. The relative amount of these tissues was estimated in each case and according to their proportions, the cases were divided into fibrous, fatty and intermediate. The number of blocks examined from each case ranged between 10 and 82. Most blocks were taken from fibrous specimens. Histological study was based on sections stained with haematoxylin and eosin (H & E) from all blocks. Selected sections were stained histochemically with alcian blue (AB, pH 2.5) before and after hyaluronidase treatment.

Immunohistochemistry performed in selected sections included staining for collagen of type III, IV and V (Sera-Lab, Sussex, UK) and for smooth muscle actin (SMA) (BioMacor, Rehovot, Israel). The avidin-biotin complex peroxidase technique was used accord-

Offprint requests to: O.Th. Anastassiades

ing to Hsu et al. (1981). The evaluation of oestrogen and progesterone receptors was done on frozen sections using ER-ICA and PgR-ICA monoclonal antibodies (Abbott Laboratories, North Chicago, Ill., USA). One part of the same tissue in all 15 cases was used for the evaluation of oestrogen and progesterone receptors by biochemical technique, for comparison of the results obtained by the two methods.

Results

Complete clinical information had been collected in 41 of the 50 cases. Data from the remaining 9 cases come only from their histology.

Clinical data

The 41 cases with a complete history included 32 cases of the juvenile type (3 of which were unilateral), 7 cases of the gravid type and 2 cases of the adult type. The menstrual cycle in all patients was normal. Endocrine disease or use of hormonal preparations was not described in any case. The body weight of the patients at the time of surgery was normal.

In the 32 juvenile cases the age of the patients at the commencement of the megalomastia is shown in Fig. 1 and the year of commencement after the appearance of menarche is shown in Fig. 2. In most cases megalomastia started at the age of 14 years with the remaining cases distributed 2 years before and 2 years after. In

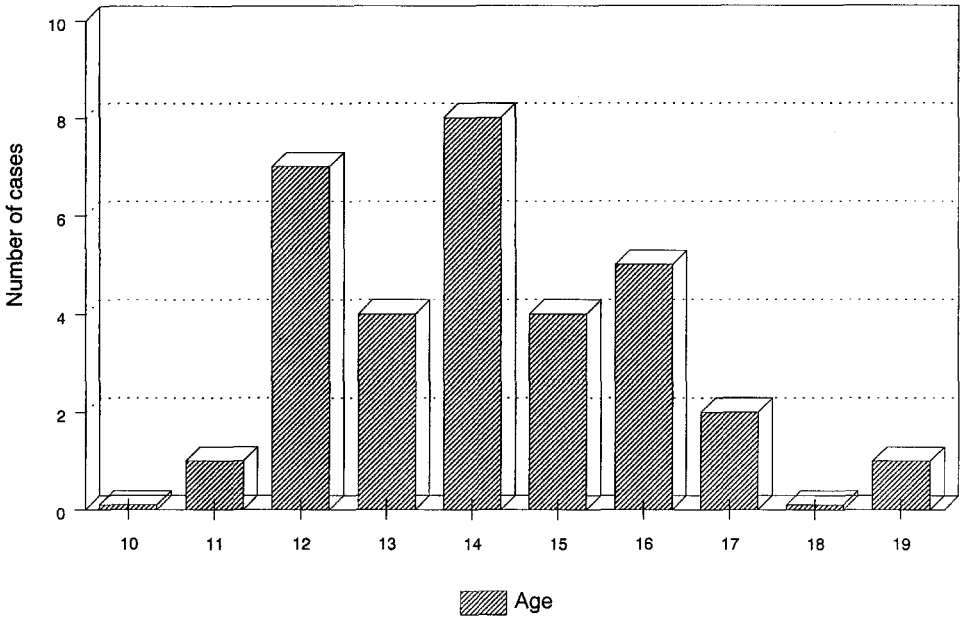

Fig. 1. Age of commencement of juvenile megalomastia

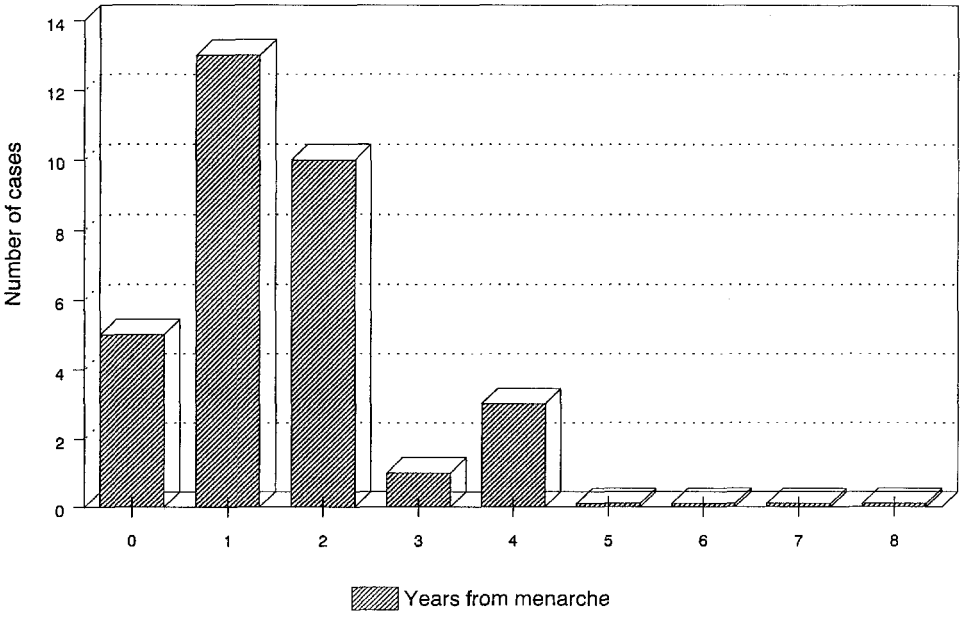

Fig. 2. Relationship between commencement of juvenile megalomastia and menarche

the great majority of cases megalomastia started either simultaneously with the menarche or 1 or 2 years after; in only 4 cases did megalomastia start after a delay of 3 or 4 years. It seems, therefore, that a close relationship exists between the beginning of the juvenile megalomastia and the menarche. The latter adjusts the distribution of the patients at various ages. In 18 of the 32 juvenile cases the megalomastia completed its development in 1–2 years, while in the remaining cases it took from 3 to 5 years. The rapidity of growth was not connected with the final size of the breasts as judged from the weight of the excised breast specimens.

Two of the patients with juvenile megalomastia, starting 1 and 3 years after menarche, showed a very slow continuous increase of breast size until their first pregnancy, which occured at the age of 18 and 20 years, respectively. The pregnancy led to a further increase, which stopped after delivery. A second pregnancy at the age of 20 and 27 years, respectively, led to a further increase in the volume of the breasts, which again stopped after delivery.

The 7 cases of gravid megalomastia had a normal menarche at between 11 and 14 years of age. In 4 patients the change started at the first pregnancy (at the age of 20 years) and in 3 patients at their second pregnancy at the age of 20 (1 case) and 26 (2 cases). A second or third pregnancy, respectively, led, in all but 1 case, to a further increase in breast size. In all patients breast growth stopped after delivery and remained unaltered thereafter. None of the patients was operated on during pregnancy. Surgery was performed between 2 and 19 years later.

Finally, the 2 cases of adult megalomastia who also had a normal menarche (at 12 and 14 years) experienced their megalomastia at 25 and 28 years of age. It completed its development at the ages of 27 and 32 years, respectively.

All patients with megalomastia of gravid type and of juvenile type associated with subsequent pregnancies stated that they were unable to lactate. Even the 1 patient with adult megalomastia at the age of 28 was unable to feed her babies after two pregnancies preceding the appearance of megalomastia.

The most frequent clinical symptoms were pains located in the shoulder and the thoracic spine, sometimes accompanied by ulcerations of the shoulder skin. Easy fatigability and decrease in personal activity was the rule. Finally, in cases with delayed surgical reconstruction, a mild degree of kyphosis was noted.

Family history of breast cancer was not present in any case. However, a family history of megalomastia was present in most cases. The 26 out of the total of 41 patients with complete clinical data had a family history of megalomastia, 12 from the paternal side, 12 from the maternal side and 2 from both families. In juvenile cases the paternal history predominated. Six of the 7 gravid megalomastias had a maternal family history. In this series 4 pairs of cases with megalomastia in the same family were also included. They were a mother and daughter and three pairs of sisters. A family history of megalomastia was present in all but one of the pairs of sisters; these were monozygotic twins. Both twins had their menarche at the age of 13 years and bilateral megalomastia started at the age of 15 years and was complete at the age of 17. Both were operated on at the age of 19 years. A similar case had been reported by Birkenfield (1932).

Pathology

A significant difference was found in the final size of the breasts among the various patients, judged by the weight of the excised surgical material. The weight ranged between 300 g and 1850 g for each breast, with no substantial differences between the specimens from the two sides. The degree of megalomastia was not connected with either the body weight of the patients or the type of megalomastia. It was closely connected with the quantity of adipose tissue present in the excised specimens. The fibrous specimens tended to have the smallest weight and the fatty specimens the highest.

Breast tissue was histologically abnormal in all cases with no substantial differences among the various types. A constant finding was the scantiness or almost complete disappearance of normal lobular units and the presence of abundant, hypocellular collagenous stroma. The lobular material was mostly represented by a few atrophic lobular ductules, scattered in isolated groups or in small clusters among the hypocellular stroma (Fig. 3). The lobular configuration was rarely retained. Lymphocytes were scant or absent. Frequently some scattered ductules had been transformed into small homogeneous balls. The interlobular ducts among the abundant collagenous stroma were mostly atrophic with occluded lumens (Fig. 4).

In rare areas a few normal or nearly normal lobular units still persisted. The stroma inside these lobular units had a rather loose texture and was positive to AB (pH 2.5), staining disappearing after hyaluronidase treatment. Some lymphocytes and occasional plasma cells were present. In other areas the stroma of lobular units was collagenous, dissecting the lobular units into segments.

Second in frequency to the lobular destruction was the presence of ductular structures which we named "juvenile units" because of their similarity to the mammary tissue at the initial stages of breast development. These units were found in all types of megalomastia, including one of the two cases of adult type. They were composed of branching ducts covered by a narrow AB-positive connective tissue mantle without terminating to lobular units (Fig. 5). Frequently, the stroma around those ducts contained lymphocytes. The "juvenile units" do not escape atrophy. The same process involving the lobular units seems to be repeated. The atrophy was characterized by occlusion of the lumens and increase and sclerosis of periductal tissue. Lymphocytes around them were severely diminished or absent. Finally, infrequent findings were small, mostly microscopical sclerotic fibroadenomas and rare histological lesions, well known from mastopathies, which were found in patients operated on

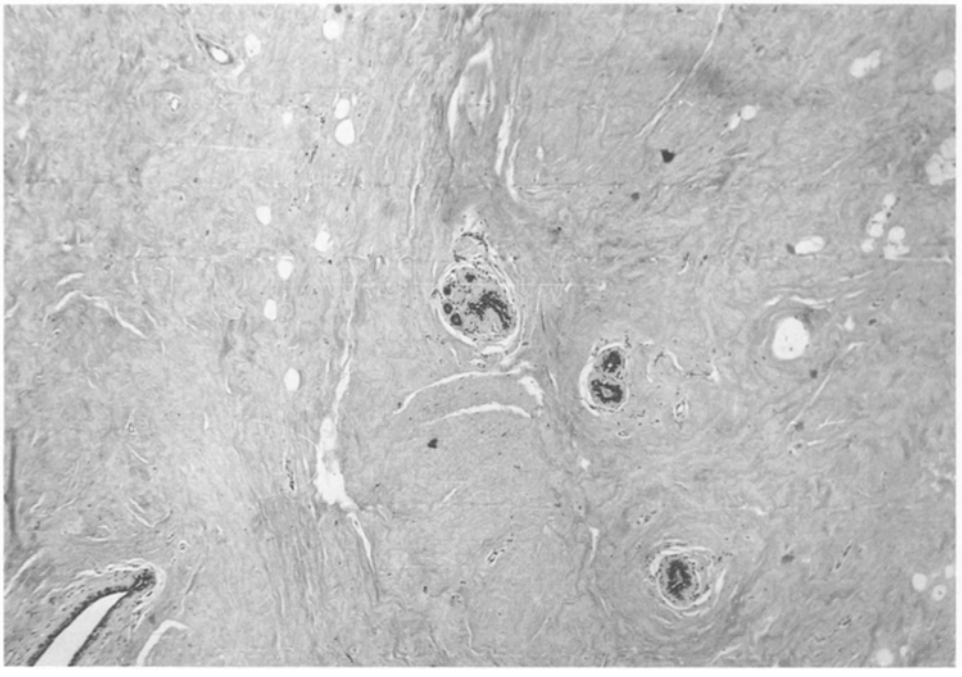

Fig. 3. Small atrophic lobular segments in collagenous hypocellular stroma. H & E, ×35

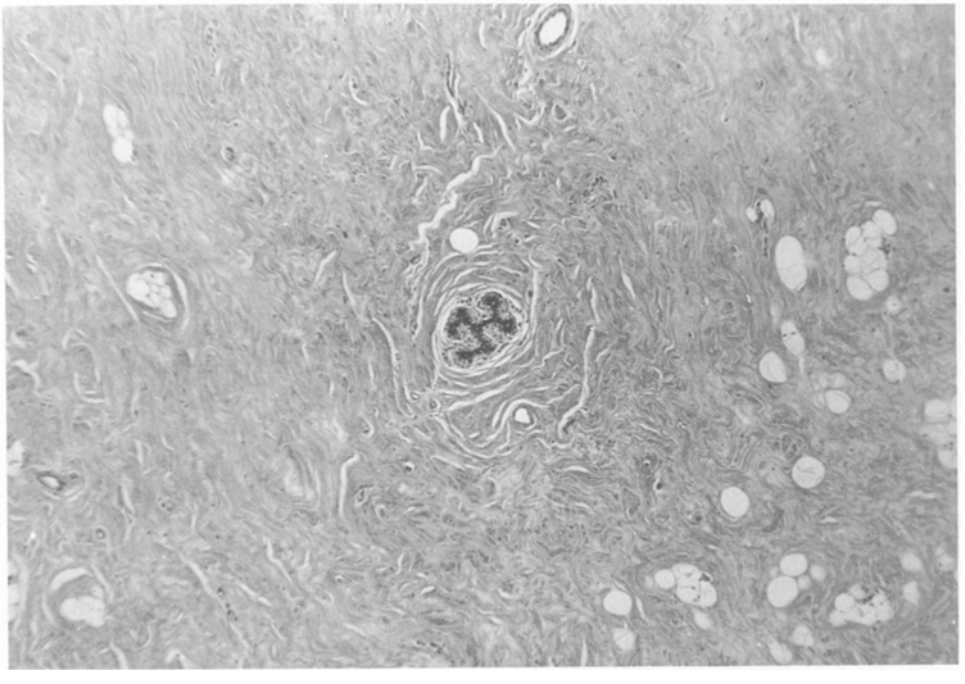

Fig. 4. Atrophic interlobular ducts among hypocellular stroma. H & E, ×35

at older ages. They included small apocrine cysts and rare foci of blunt duct adenosis and sclerosing adenosis.

Immunohistochemistry showed that lobular units when present were within normal limits. Both lobular ducts and ductules exhibited well-developed basal membrane, positive to collagen type IV and type V antibody (Fig. 6). A continuous layer of myoepithelial cells positive to SMA antibody was also present. In remmants of destroyed lobular units the hypocellular collagenous stroma was reactive to collagen type III antibody. The same immunohistochemical findings were repeated in "juvenile units" either developing or involved in the process of atrophy and fibrosis.

Immunohistochemical determination of oestrogen and progesterone receptors was performed in 15 cases from which fresh tissue was available. These cases included all types of megalomastia, 13 being of juvenile, 2 of gravid and 1 of the adult type. The age of the patients at the time of surgery ranged between 19 and 42 years. All cases proved negative for oestrogen receptors in contrast with the positive controls. Progesterone receptors were positive in all cases, with the strongest

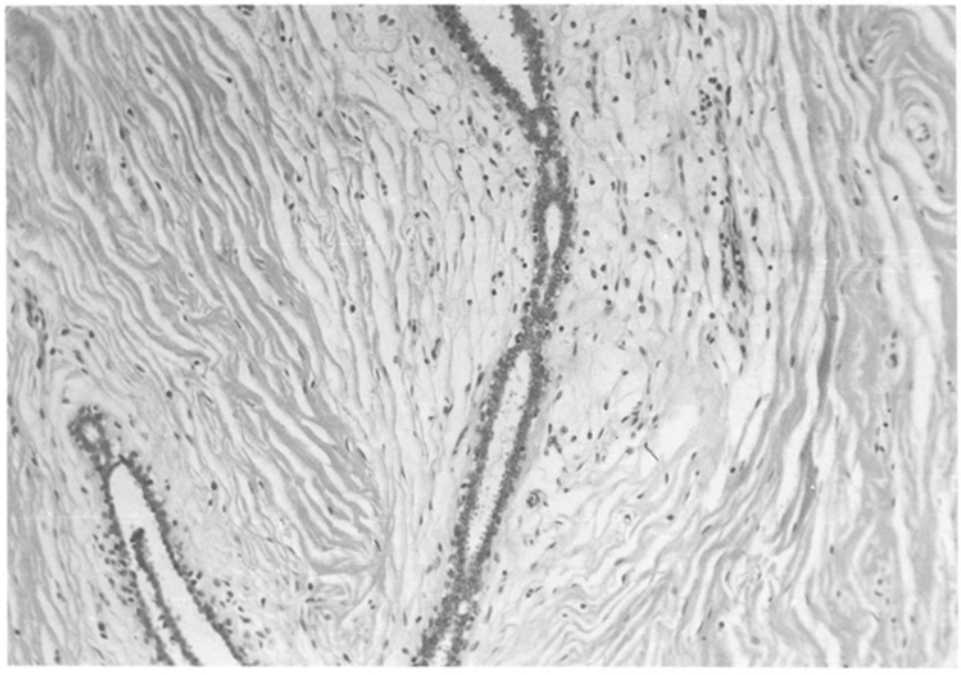

Fig. 5. "Juvenile unit". H & E, ×150

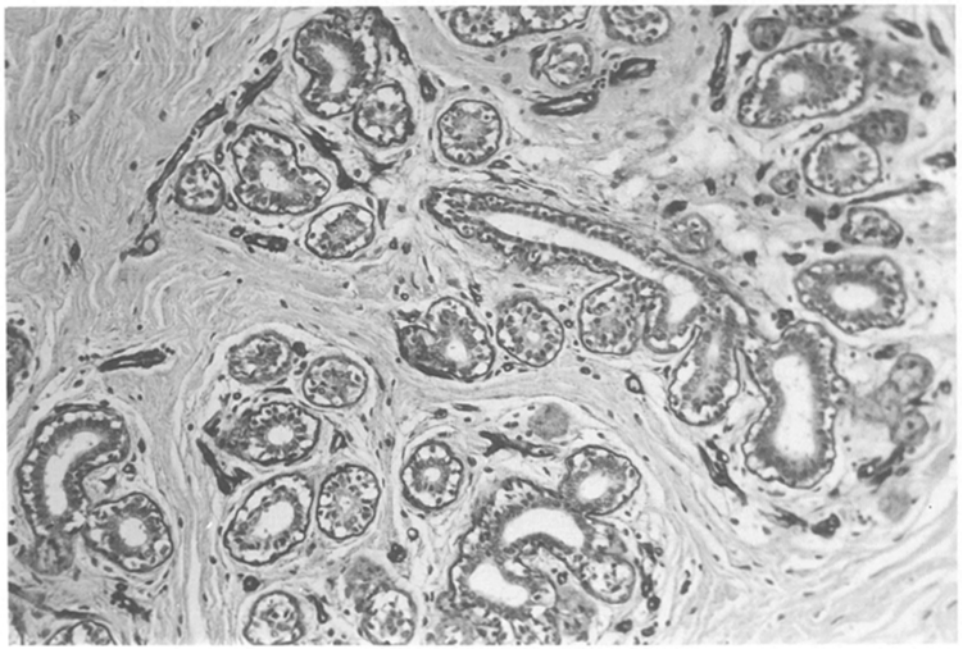

Fig. 6. Lobular unit with partial preservation of normal lobular configuration. Basement membrane positive to collagen IV antibody. Some lobular ductules transformed into small homogeneous balls. Avidin-biotin method, ×150

positivity expressed by "juvenile units" (Fig. 7) not involved in the process of atrophy and fibrosis.

Biochemical determination of hormonal receptors was performed in part of the same tissue used for the immunohistochemical determination. Oestrogen receptors were negative in all cases, with levels ranging from 0 to 10 fmol/mg protein. Progesterone receptors were negative in 10 cases, positive (20–32 fmol/mg protein) in 3 cases and strongly positive (74 and 219 fmol/mg protein) in 2 cases. These last 2 cases were operated on at the greatest ages compared with the other patients of the series. One patient was 41 years old, with juvenile megalomastia completing its development at 16 years, and the other was 42 years, with gravid megalomastia completing its development at 21 years.

Discussion

The greater frequency of the juvenile type of megalomastia referred to in the literature was confirmed by our findings. It also confirmed the rarity of adult and unilateral megalomastia. The aetiology of this peculiar syndrome is unknown. Hormonal disturbances have been

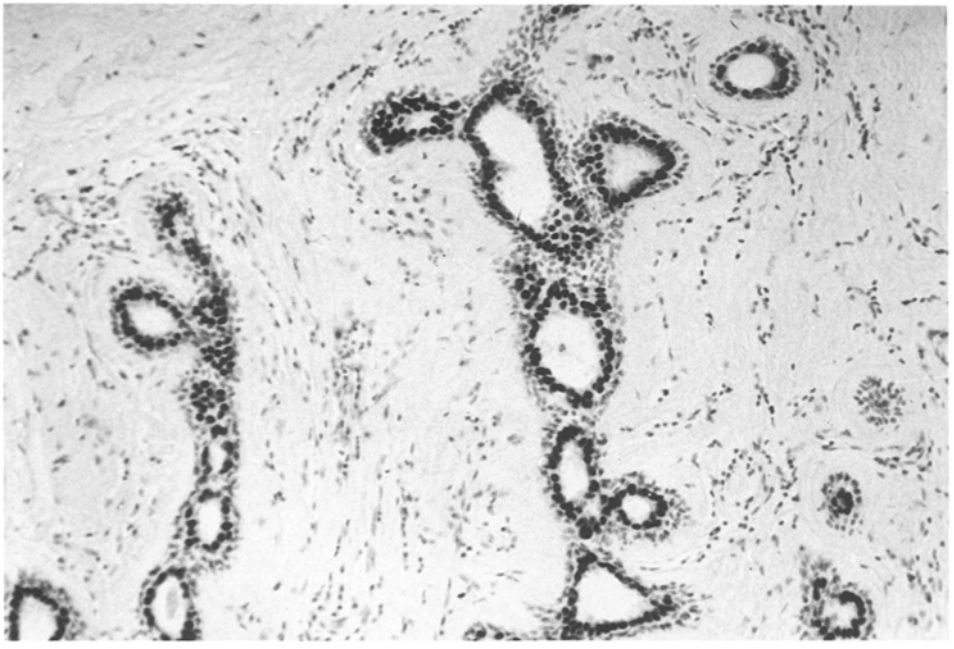

Fig. 7. Positive progesterone receptors in the epithelial cells of "juvenile units". Lymphocytes in the stroma. PAP method, ×150

implicated as causative factors by some authors (Gargon and Coldwyn 1987; Geschickter 1945; Griffith 1989; Lafreniere et al. 1984; Van Heerden et al. 1988). However, evaluation of hormonal levels in the peripheral blood of the patients did not show substantial abnormalities (Boyce et al. 1984; Gavrilescu et al. 1977; Lafreniere et al. 1984; Ryan and Pernoll 1985; Sagot et al. 1990; Tchabo and Stay 1989). Data concerning the hormonal profile of the peripheral blood were not available in our patients. Menstrual or other endocrine disturbances, however, were not present in any of the patients. A possible relationship of the syndrome to a peculiar responsiveness of the mammary gland to normal hormonal stimuli has also been proposed (Gavrilescu et al. 1977; Geschickter 1945; Lewis and Geschickter 1934; Mayl et al. 1974). A predisposition of the breasts to develop the syndrome cannot be excluded, inasmuch as a family factor is implicated in the process. The presence of a family history is referred to sporadically in the literature (Lafreniere 1984; Strombeck 1964). The complete analysis of the family factor in this study proved its presence in more than half the cases, deriving from either family or from both. The close connection of the maternal history to the gravid type of megalomastia is of interest. The significance of the family predisposition for the development of the syndrome is further supported in this series by the presence of members from the same families.

Some authors agree that gravid megalomastia appears more frequently during the second pregnancy (Beischer et al. 1989; Leis et al. 1974; Miller and Becker 1979; Stavrides et al. 1987; Strombeck 1964; Williams 1957). Such a relationship was not apparent in our patients. It seems worthwhile, however, to mention that all juvenile and gravid megalomastias developed in the young. It appears that youth is an important factor in the development of megalomastia, since even in the very rare adult type of megalomastia, the 2 patients of our series experienced the beginning of their megalomastia at 25 and 28 years of age.

A significant datum resulting from our series is the complete lack of the capacity to lactate in all patients with gravid megalomastia and also in 4 patients with juvenile megalomastia with subsequent pregnancy. One patient with adult megalomastia with two pregnancies preceding the appearance of the syndrome reported a complete lack of lactation in both pregnancies. This inability to lactate is also referred to by Bässler (1978) and can be easily interpreted in histological terms. The mammary glands in all 50 cases examined histologically were mostly devoid of or included very few normal lobular units.

Our histological data indicate that the phenomenon of megalomastia, irrespective of the type, is characterized by a biphasic histological picture, containing an atrophic and a hypertrophic component. The atrophic component consists of gradual destruction of the lobular units and, in extreme cases, of the interlobular ducts with simultaneous development of abundant hypocellular connective tissue. The increase in the collagenous stroma of the breasts is also referred to by many authors (Bauer et al. 1987; Beischer et al. 1989; D'Alessandro and Taylor 1986; De Castro 1977; Fisher and Smith 1971; Leis et al. 1974; Zienert 1990). We found that the quantity of the collagenous tissue is connected with the degree of epithelial atrophy. This connection indicates that the two processes advance in parallel and express the same course. The steady expression of type III collagen by the connective tissue stroma around atrophic lobular elements indicates that the stromal component of the gland has also lost its functional activity. More advanced lobular atrophy and fibrosis was found in the youngest patients. It is, in fact, impressive that young adolescents, a few years after menarche, have huge

breasts with their lobular material nearly completely destroyed. The hyperplastic component, described as "juvenile unit", was the second commonest finding and was present in 16 cases, including 1 of the 2 of adult type. We think that the discovery of both those elements in histological sections is diagnostic of megalomastia. We do not know whether the development of the "juvenile units" indicates an effort to counterbalance the destruction of the lobular component of the breast. If so, it is without effect, as juvenile units follow the same process of atrophy and fibrosis.

The remaining histological alterations found in megalomastia seem not to be directly related to the main pathological process. Data from the literature (D'Alesandro and Taylor 1986; Lewis and Geschickter 1934; Stavrides et al. 1987) consider fibroadenomas to be a common feature in megalomastias. We did not confirm this. The very rare foci of sclerosing adenosis, blunt duct adenosis and microcysts found in patients of older ages co-incide with the age of appearance of mastopathic lesions in the breast.

Our findings from the study of hormonal receptors deserve discussion. The presence of progesterone receptors can be easily explained as during puberty and pregnancy the mammary epithelium is particularly sensitive to progesterone stimulation. The intense positivity of the "juvenile units" further indicate that these structures probably constitute an abortive tendency for substitution of the destroyed lobular units. There is a lack of analogous immunohistochemical data to compare with our findings but recently some authors (Boyce et al. 1984; Gargan and Coldwyn 1987; Lafreniere et al. 1984; Van Heerden et al. 1988) have reported biochemical determination of both hormonal receptors with negative results. We consider that the difference in progesterone receptors found between immunohistochemical and biochemical determinations can be attributed to the great amount of stroma present in the specimens which affects the biochemical analysis. We are unable to interpret, however, the high levels of progesterone receptors found biochemically in the 2 older patients. It is well known that the lobular units appear later in breast development after the establishment of the biphasic menstrual cycle and the influence exerted by progesterone. The appearance of juvenile megalomastia 1–4 years after menarche coincides with this period. In gravid megalomastias the syndrome starts with the occurrence of pregnancy, with progesterone implicated at the initial stages of breast development. It is clear that in both conditions developmental stimuli are exerted upon breasts with a consequent increase of their size. This increase of breast size appears at times when it might be expected, but it takes on enormous dimensions and is accompanied by extensive destruction instead of the development of functional lobular units.

The severe damage of breast histology, with functional units predominantly involved, is a complicated and obscure condition which deserves further investigation. Perhaps an immunopathological mechanisms is suggested by the presence of lymphocytes at sites of epithelial cell destruction.

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