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Review Article

Adenomyosis and Endometriosis Have a Common Origin

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Abstract

The presence of epithelial cells in the peritoneal cavity and within the myometrium was described during the second part of the 19th century and was given the name "adenomyoma". Then, with the identification of peritoneal endometriosis in the 1920s, adenomyosis became a separate nosological entity. For decades, the two abnormalities have been considered separate benign proliferative conditions of the female reproductive tract with a different clinical profile. More recently, however, evidence has been accumulated indicating that these two diseases have in common an endometrial dysfunction involving both eutopic and heterotopic endometrium causing a reaction in the inner myometrium (the so-called myometrium junctional zone (JZ)). It therefore seems that adenomyosis and endometriosis share a common origin in an abnormal eutopic endometrium and myometrium JZ. It is therefore no surprise that both conditions are associated with obstetrical disorders, such as spontaneous preterm delivery and premature preterm rupture of the membranes, which may have roots in a disturbed decidualization and placentation process.

Keywords: endometriosis, adenomyosis, junctional zone myometrium, deep placentation

Introduction

Scientific investigation of historical documents can yield important information for improving our knowledge of disorders, like endometriosis and uterine adenomyosis. In addition, when searching to understand how endometriosis and uterine adenomyosis were initially described, it is important to understand the morphological and clinical presentation of these disorders. In the past, the enigmatic terminology used to describe the presence of epithelial cells within the peritoneal cavity rendered interpretation difficult, particularly in the older literature [1]. Indeed, at the end of the 19th and during the first quarter of the 20th centuries, both the conditions were described together under the name "adenomyoma" [2]. In 1918, Lockyer defined an adenomyoma as "a new formation composed of gland elements, hyperplastic cellular connective tissue, and smooth muscle", but made no mention of the fact that the glands are endometrial in nature[3]. Today, uterine adenomyoma and endometriosis are defined as the presence of endometrial-like tissue outside the uterine mucosa, respectively, in the myometrial wall and outside the uterus and are considered as separate pathological entities.

Contrary to this commonly held belief, we have recently argued that endometriosis and uterine adenomyosis are phenotypes of one modern gynaecological syndrome[4]. We believe that both Sampson's hypothesis of "menstrual regurgitation" for the genesis of endometriosis [5] and Cullen's observation of a direct connection between the adenomyotic tissue and the mucosa of the uterine cavity [6] remain valid and have

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been amply confirmed. At the same time, we hold that two important additional factors play a pivotal role in the pathogenesis of both adenomyosis and endometriosis: modifications in the so-called "junctional zone" (JZ) or inner portion of the myometrium and a series of functional changes in the eutopic, as well as heterotopic endometria of women suffering from these diseases. Finally, evidence is being accumulated that a connection exists between endometrium and inner myometrium abnormalities and some of the major obstetrical syndromes through a defective deep placentation [7].

Historical overview

In 1999, Vincent Knapp [8], on the basis of eleven historical documents published between 1695 and 1795, put forward the hypothesis that endometriosis had been identified over 300 years ago. The problem is that recent scrutiny of the original manuscripts does not support this hypothesis. The cases described included inflammation that produced pus, a uterine wound or an erosion that was linked to manipulation, an abortion, or a syphilitic lesion. In addition, without a microscope, these early authors had no way to even guess the presence of endometrial tissue outside the uterus.

More solid is the hypothesis that the first ever description of endometriosis was made by Carl Rokitansky, who, in 1860 [9], observed endometrial glands in the myometrium and provided the first histological description of what was later called "uterine adenomyoma". The problem is that he designated this finding as "cystosarcoma adenoids uterinum'', a clear misinterpretation of a non-neoplastic disease.

Later on, the presence in the peritoneal cavity of epithelial glands surrounded by muscular fibres was designated as "adenomyoma" [10] and considerable controversy arose as to the origin of the glands in uterine adenomyomata; famous pathologists such as von Recklinghausen [10] were convinced that adenomyoma was the result of displacement of wolffian or mesonephric vestiges. At the same time, he was the first to distinguish between extrauterine and intrauterine adenomyoma and insisted that they were entirely separate entities, with only cases arising within the uterine wall and possessing glands being derived from the uterine mucosa. It was then a surgeon, Thomas Cullen, who, in 1908, described for the first time both the morphological and clinical picture of uterine adenomyomata [6]. Cullen interpreted the typical adhesions on the posterior side of the ovary as a mild degree of pelvic peritonitis; he clearly described adhesions associated with endometriosis at the hilus of the ovary. Although W.W. Russel [11] was the first to describe a case of ovarian endometrioma, it was Cullen who connected them to adenomyoma and drew a scheme with the classic sites of adenomyoma/ endometriosis lesions in the pelvis [12].

Discovering a spectrum of morphological appearances

Adenomyotic lesions

Thomas Cullen described "adenomyomas" involving ectopic endometrial-like tissue in the myometrial wall, recto-vaginal septum, hilus of the ovary, uterine ligaments, rectal wall, and umbilicus [12]. There is no doubt that Cullen considered uterine adenomyoma, ovarian endometriosis, and deep endometriosis as one disease characterized by the presence of adenomyomatous tissue outside the uterine mucosa.

In the 1940s, endometriosis was described as not an uncommon disease, with various clinical appearances. At times, a widespread distribution of lesions within the peritoneal cavity was noted. The majority of the lesions occurred on the peritoneum, cul-de-sac, recto-vaginal septum, and ovaries. Less frequent locations included the umbilicus, the round ligaments, recto-sigmoid, and laparotomic scars. Larger lesions may consist of a more or less solid tumor, an adenomyoma, or may be in the nature of a haemorrhagic cyst. In this connection, Benson and Sneeden argued in 1958 that confusion had developed because of the unfortunate and illogical inclusion of uterine adenomyosis with pelvic endometriosis, which according to them, only occasionally coexist [13].

Peritoneal endometriosis

With the introduction of laparoscopy in the 1960s, a golden tool became available for visual diagnosis and surgical therapy of endometriosis. As a result, endometriosis was divorced from the uterus and research became focused on how fragments of menstrual endometrium can implant on peritoneal and ovarian surfaces, provoke adhesions and retraction, and involve the underlying tissues to form deep or pseudo-deep endometriosis.

It became evident that peritoneal endometriosis has multiple appearances including microscopic foci, early-active (red, glandular, or vesicular), advanced (black,

puckered), and healed (white, fibrotic) appearances. These lesions may represent replacement of mesothelium by an endometrial epithelium or endometrial polyp formation [14,15]. However, the anatomic distribution of ectopic endometrium, as assessed by laparoscopy in a series of 182 consecutive patients, supported Sampson's hypothesis of retrograde menstruation as the primary model of development of endometriosis [16]. Consecutive laparoscopic observations in the same patient [17] suggested that early lesions appear and disappear "like mushrooms on the peritoneal surface". Awareness of the existence of subtle endometriosis produced an increase in its diagnosis, although clinical significance of early lesions remained controversial [18–20].

Ovarian endometrioma

As mentioned above, W.W. Russel [11] was the first to describe, in 1899, a case ovarian endometrioma, although in his paper he mentions the fact that "gland-like spaces" in the ovary had already been described. Following this first case, Semmelink and De Joselin de Jong described a case with a structure "similar to that of uterine stroma", that they considered as a tumor arising from Wolffian remnants [21]. A third early case of "uterine mucosa in remaining ovary after hysterectomy" was published by Casler in 1919 [22], who described the "entire cyst, or uterine cavity as it really is", as entirely lined by "a single layer of tall columnar epithelium of the uterine type". He added that "in places the cilia can be made out". A further case was published by Norris in 1921 [23]; he attributed his case to the presence of Müllerian remnants; obviously, he was not aware of Sampson's fundamental paper published the same year [24].

It was only 30 years later that a detailed, precise description of endometriomas appeared thanks to Hughesdon [25] who, in 1950, proved that most ovarian endometriomas were in fact pseudocysts with essentially a similar structure. The ovary is adherent to the posterior side of the parametrium, the inside is constituted by invaginated ovarian cortex, endometriotic tissue is found at the site of adhesion, and a thin layer of superficial endometrium-like tissue extends to cover partially or fully the invaginated cortex. The concept of invagination was supported by four features of the ovarian endometriomas*:* first, primordial and ripening follicles are found in the wall of the cyst; second, the ovary does not invaginate uniformly, but remains on one side more or less normal; third, on the extended side the wall is relatively thin and the attenuation of layers on this side is usually too great to reveal the original structure and finally, the identity of the cortex on the inner side is frequently obscured by smooth muscle metaplasia. Hughesdon concluded that ectopic endometrium does not simply erode its way into the ovary: the ovary is actively invaginated, thus, providing a pseudo-uterus.

Divorcing Adenomyosis from Endometriosis

Another surgeon, John A. Sampson provided the first theory on how endometrial glands and stroma could implant in the peritoneal cavity. He observed that in women operated at the time of menstruation, peritoneal lesions showed endometrial shedding and were bleeding similarly to what happens in eutopic endometrium, a functional proof that the tissue was of endometrial origin [24]. Sampson did not believe that these ectopic foci originated from ruptured ovarian endometrioma and, in 1927, he enunciated his theory that "menstrual regurgitation" of endometrial cells in the peritoneum was at the origin of lesions he called "endometriosis" [6]. Not everyone agreed with Sampson and, in 1932, Emil Novak [26] developed a different theory: he postulated that the occurrence of differentiation's anomalies in the epithelium of various segments of the genital canal indicated the tendency towards variability of these genital epithelia under certain conditions. He argued that this tendency reflected their common origin from the same mother tissue, the coelomic epithelium. In his view, it seemed unnecessary to invoke the doctrine of "transplantation" to explain endometriosis, since types of differentiation's transitions may be seen in ovarian endometriosis, including a tubal epithelium with or without stroma, a uterine epithelium with or without glands and with or without stroma, an endometrium with or without physiological reactivity, and with or without haemorrhage. Novak believed that his theory would support the germinal epithelium origin of serous cystadenomas and explain how tubal pregnancies could develop. Besides the above-mentioned two theories, during the following decades several additional hypotheses were presented to explain the pathogenesis of endometriosis, though no single theory could explain all presentations.

Irrespective of its pathogenesis, clinical diagnosis remained elusive until the introduction of laparoscopy in the 1960s, provided a new, fundamental tool bacame available for the diagnosis and the treatment of the condition.

Sampson's theory had one major consequence: it separated endometriosis in its various forms and manifestations from adenomyosis and, although the two disorders were occasionally referred to as endometriosis interna and externa, they were considered separate diseases.

Reunifying the two conditions

In 1951, Javert [27] developed a composite theory involving both the conditions again. He considered the growth of ectopic endometrium to be similar to a "benign metastasis", since the spread of the endometrium is essentially the same as for endometrial carcinoma, with direct extension into lymphatics or blood vessels of the myometrium, or between the muscle bundles, thereby producing adenomyosis uteri. Exfoliation and implantation of endometrial cells at menstruation, during curettage or from a focus in the tube produced lesions on peritoneal surfaces; and lymphatic and venous spread produced lesions in adjacent or distal organs. He even explained the observed increase in the number of cases by the tendency towards smaller families, widespread use of contraception, fewer cervical dilatations, fewer uterine suspension operations, and more intravaginal tampons during menstruation. Like many other physicians of his days, he believed that pregnancy was the best prophylactic and curative treatment for endometriosis, since it interrupts the cyclical homeoplasia during which time the endometrium lies dormant.

A major push towards the identification of a common origin for adenomyosis and endometriosis came from the discovery of a distinct functional zone in the portion of myometrium adjacent to the endometrium, the already mentioned JZ.

Endometrium and JZ myometrium share a paramesonephric embryonic origin, while the outer myometrium is of non-paramesonephric origin. The notion that the inner portion of the human myometrium constitutes a separate entity within the uterine musculature is more than a century old and was put forward in 1898 by Werth and Grusdew [28] who called it "archimyometrium". Notwithstanding this early description, it was only with the emergence of Magnetic Resonance (MR) imaging [29] that the inner myometrium was confirmed to be a distinct structure, not only in terms of its embryonic origin but also in its specialized functions [30,31]. It was recognized that considerable variations exist in thickness and visibility of the JZ between individuals, depending on hormonal status (e.g. menarche, postmenopausal, phase of menstrual cycle, and use of oral contraceptives). This variability has made it difficult to define the "normal" uterine zonal anatomy on MR imaging [32,33].

Initially, an increased thickness of the JZ has been correlated to the presence of adenomyosis and thicknesses of 12 mm or more have been considered a sort of golden standard for a non-invasive diagnosis of uterine adenomyosis [34.] Histologically, adenomyosis is currently diagnosed when the distance between the lower border of the endometrium and the affected myometrial area is over one-half of a low-power field (2.5 mm) [35]. At the same time, in hysterectomy specimens from normal parous women endometrial tissue can be found at the site of previous placentation penetrating deeper than 2.5 mm; therefore, basing the prevalence of uterine adenomyosis only on such histological criterion, may lead to overestimation in hysterectomy specimens from parous women [36,37]. Matalliotakis [38]has proposed two ways to get around this problem. The first is to determine the existence of myometrial hypertrophy around foci of adenomyosis. Such differentiation is not seen at the JZ myometrium. The second is to measure the distance between the endometrium and the closest adenomyotic foci; this should be more than one third of the total thickness of the myometrium.

Today, evidence is accumulating that also the presence of endometriosis is accompanied by JZ abnormalities and there is extensive literature demonstrating that endometriosis, particularly in more severe stages, is associated with structural changes in the JZ or inner myometrium, including increased thickness and adenomyosis [39–42]. In addition, studies of the JZ in women with endometriosis showed that modifications leading to the development of adenomyosis, represented by an increased diameter of the dorsal JZ of the uterus at magnetic resonance imaging, had already commenced early in the third decade of life and, in these women, progressed steadily during the fourth decade [43]. Women without endometriosis showed almost no signs of alterations leading to adenomyosis up to the age of 34 years, whereas beyond this age, in both groups a marked increase could be observed, thus representing a common phenomenon in the age-related patho-physiological continuum of adenomyosis.
At this stage in our knowledge, it seems logical to state that the two conditions are characterized by the

presence of epithelial, stromal, and smooth muscle cells, although the dominant cells may be stromal and epithelial cells in endometriosis and smooth muscle cells in adenomyosis.

Notwithstanding the importance of JZ alterations in considering adenomyosis and endometriosis as two phenotypes of the same disorder, the most important argument for a reunification of their pathophysiology is represented by a number of similarities observed in functional and molecular aberrations of the eutopic endometrium in both situations. These include immunological abnormalities, invasive properties, decreased apoptosis, alterations in expression of specific genes and proteins, and increased cytokine production [4].

Similar immunological abnormalities have been observed in women with adenomyosis and endometriosis both in eutopic and ectopic endometria: expression of HLA – DR antigen is significantly lower [44] and there is an increased number of T cells, a higher expression of IFN-γ, and enhanced antigen presentation in ectopic compared to eutopic[45]. With regard to apoptosis, an elevated stromal Bcl-2 (which blocks the apoptotic pathway expression) in ovarian endometriotic lesions could have implications for the growth and survival of ectopic endometrial tissue[46]. In endometriosis and adenomyosis there is an increased oxidative stress and depletion of antioxidants; these phenomena may contribute to excessive growth of endometrial stromal cells. Finally, local oestrogen production can take place in both eutopic and heterotopic endometria of women with adenomyosis and endometriosis [47] and this phenomenon is associated with polymorphism in the oestrogen receptor–alpha (ERα) [48]

Recently, a comprehensive profiling of gene expression differences between the ectopic and eutopic endometrium in endometriosis patients was carried out by Wu et al. [49], who found 904 genes/ESTs that are differentially expressed. Finally, in women with endometriosis a number of proteins are dysregulated (50); interestingly, the gene COMT (encoding catechol-*O*-methyltransferase one of several enzymes that degrade catecholamines) significantly influences the risk of adenomyosis, but not endometriosis, at least in Chinese women [51].

Adenomyosis, endometriosis and obstetrical complications

Recent clinical data suggest that both endometriosis and uterine adenomyosis increase the risk of a spectrum of pregnancy complications. The mechanism of these complications has been related to defective decidualization and deep placentation [7]. Based on pre-pregnancy imaging, Juang et al. [52] reported that adenomyosis is an important risk factor for spontaneous preterm delivery and preterm premature rupture of the membranes. Fernando et al. [53] found that the rates of preterm birth and small for gestational age doubled in infertility patients with ovarian endometriomas who required assisted reproductive technologies (ART). According to Stephansson et al.[54] endometriosis is a risk factor for preterm birth, irrespective of the type of technique of assisted reproduction performed.

Conclusions

A large number of investigators over more than 150 years have contributed to the path leading to the identification of the diseases we today call adenomyosis and endometriosis; in spite of this the resulting picture is still somewhat confused and the nature of these benign abnormalities is still unclear.

Nonetheless, we believe that today it can be stated that the primum movens for both anomalies lies in an abnormal endometrium, with an increased ability to survive and implant itself either in the myometrium of in the uterine cavity.

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