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Atypical ductal hyperplasia of the breast – a diagnostic and therapeutic problem

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Introduction. Atypia is considered to be a risk factor for subsequent breast cancer, increasing the risk of developing malignancy 3-5 times. The diagnosis and treatment of atypical hyperplasia of the mammary gland is still controversial.
Aim. The aim of the study was to perform a retrospective analysis of all cases of atypical ductal hyperpasia and to discuss the treatment of atypical ductal hyperplasia basing upon our own experiences and current publications regarding this subject.
Method. 789 mammotomic biopsies of small breast lesions had been peroformed: 512 ultrasound-guided and 277 stereotactic.
Results. In case of 24 patients ADH was found in the histological specimen. There were 10 cases (1.9%) of atypical ductal hyperplasia in the ultrasound-guided biopsy group and 14 cases (5.0%) in the stereotactic biopsy group. Pathological examination of open biopsy specimens revealed 7 cases of fibro-cystic lesions, 3 cases of mild hyperplasia, 2 cases of atypical ductal hyperplasia and 2 cases of invasive carcinoma (ductal carcinoma and papillary carcinoma respectively). 10 (41.6%) patients with ADH had not been operated as they refused informed consent to an open surgical biopsy although they had been informed about the increased risk of breast malignancy.
Conclusion. Upon our own experiences and current literature we recommend performing an open surgical biopsy in patients with atypical hyperplasia found in the mammotomic biopsy specimen.

Key words: atypical hyperplasia, breast cancer, mammotomic biopsy

Introduction

The differentiation between atypical ductal hyperplasia (ADH) and in situ ductal carcinoma (DCIS) of the breast is very difficult and may depend on the subjective judgment and experience of the pathologist. Several studies have demonstrated that diagnosis of atypical ductal hyperplasia of the mammary gland is associated with a relatively high risk of breast cancer [1]. The pathogenesis of breast cancer may be heterogenous. Not every case of atypical hyperplasia progresses into invasive cancer [2, 3]. According to one model of breast tumor genesis, atypical hyperplasia develops from normal ductal cells. Further accumulation of genetic abnormalities leads to the development of carcinoma.

Since atypical hyperplasia increases the risk of developing invasive carcinoma 3-5 times, it requires establishing treatment standards. Although many authors recommend surgical treatment in those patients, we still lack algorithms regarding the size of excision.

The problem with diagnosing ADH begins with the differences in understanding what atypia means. In 1916 Bloodgood introduced the term “borderline” for lesions about which “both the surgeon and pathologist are in doubt” [4]. Pathologists agree with a concept that atypical proliferative lesions exhibit some, but not all, features of carcinoma in situ. One definition characterizes ADH as having the cytological features of the non-necrotic forms of intraductal carcinoma with the changes may involve two or more ducts or ductules but measuring less than 2 mm in aggregated diameter [5] Other authors do not include a measured dimension in their definition [6]. Some pathologists suggest that ADH and DCIS should form one diagnostic category termed “mammary intra-epithelial neoplasia (MEN)” [7].

Borderline epithelial lesions, such as ADH, are very problematic and require very close cooperation between the pathologist, the radiologist and the surgeon.

The aim of this study was to perform a retrospective analysis of all observed cases of atypical ductal hyperpasia and to discuss the treatment of atypical ductal hyperplasia basing upon our own experiences and current publications regarding this subject.

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Material and methods

Between January 2001 and May 2004, 789 mammotomic biopsies of small breast lesions had been performed at the Regional Unit of Early Diagnosis of Breast Diseases at the First Department of General and Gastrointestinal Surgery in Krakow (Poland). Core biopsies were performed with the use of a prone multidirectional 11-gauge vacuum-assisted device with a minimum of 6 passes.

512 biopsies were ultrasound-guided and 277 were stereotactic. The ultrasound-guided biopsies were performed in patients with small (about 10 mm and less in diameter), solid lesions, not visualized in mammography and in patients with dense breast tissue in whom mammography is often falsely negative. Stereotactic biopsies were performed in patients with suspicious microcalcifications found in screening mammography. In case of stereotactic biopsies radiographs of the specimen were taken in order to confirm the inclusion of representative tissue. Only patients found to have atypical ductal hyperplasia on pathological examination were included in the analysis.

All histological specimens were stained with hemotoxilin-eosin and the slides were reviwed by a fellow pathologist from the Department of Pathomorphology of the Collegium Medicum in Krakow, Poland.

All breast biopsies were performed under local anesthesia. After the removal of the specimen titanium markers were placed in the excised area. The patients were discharged after an observation period of one hour. On the next day all patients underwent control ultrasonography in order to monitor any post-biopsy complications.

The patients requiring further surgical treatment were operated at the 1st Department of General and Gastrointestinal Surgery in Krakow, Poland. Women with benign breast lesions on mammotomic biopsy had regular follow-up visits at the Regional Unit of Early Diagnosis of Breast Diseases. The first control examination after the biopsy was held three months after the procedure. The following visits were held at one-year intervals.

Results

Between January 2001 and May 2004 at the Regional Unit of Early Diagnosis of Breast Diseases of the First Department of General and Gastrointestinal Surgery in Krakow, Poland we had performed a total of 789 consecutive vacuum-assisted core biopsies (512 ultrasound-guided and 277 stereotactic) in 789 women.

Patients with atypical ductal hyperplasia found in the specimen were analysed. This group consisted of 24 women. In the entire group of 789 biopsied patients 10 (1.9%) ADH patients had undergone ultrasound-guided biopsy and 14 (5.0%) – stereotactic biopsy. The mean age of this patient group was 54 years (range: 30-72). 13 (54.2%) biopsies were obtained from the right breast, and 11 (45.8%) from the left breast.

Only 4 (12.5%) women presented with symptoms prior to diagnosis. Three patients had a palpable lump of less than 10 mm in diameter while one woman complained of pain in the breast. The remaining 20 patients (87.5%) were asymptomatic and the diagnosis had been made in the course of mammographic screening or ultrasound. The lumps which were palpable during physical examination were visualized as hypoechogenic well-circumscribed areas in the ultrasound examination and were not well visualised in the mammographic radiographs. We observed complications in 3 cases, (12.5%); these patients had heamatomas and in the case of one of these patients surgical intervention was necessary.

The mean age at first menstruation was 14 years (range: 12-17). Ten women were premenopausal at the time of diagnosis. The mean age at last menstruation in the postmenopausal women was 50.6 years (range: 46-57). The mean number of pregnancies was 2.2 (range 0-5). Nine patients (37%) had hormonal therapy (from 1 to 15 years). Three women (12.5%) had a family history of a first-degree relative with breast cancer.

Ten of the ADH patients (41.6%) had undergone no further surgical treatment. These women had refused informed consent to open surgical biopsy, although they had been informed about an increased risk of breast malignancy. These women were followed-up at six-month intervals. No ultrasound or mammography abnormalities had been found in those patients. As ADH also increases the risk of cancer in the contralateral breast it is necessary to control both breasts regularly. Mean follow-up time was 42 months (range: 19-64 months). The remaining 14 women (45.9%) underwent open biopsy after a localizing wire had been placed in the preset area under ultrasound or mammography control. Pathological examination of the specimens revealed 7 cases of fibro-cystic lesions, 3 cases of benign hyperplasia, 2 cases of atypical ductal hyperplasia and 2 cases of invasive carcinoma. (1 case of ductal carcinoma and one case of papillary carcinoma). Of these patients one underwent modified radical mastecomy, while the patient with papillary carcinoma refused either radical treatment or regular follow-up visits and was lost from the analysis.

Discussion

Atypical ductal hyperplasia is a quite rare but a very problematic diagnostic and therapeutic problem. Atypia is considered to be a risk factor of subsequent breast cancer, increasing the risk of developing a malignancy by some 3-5 times. According to some authors it is not only a risk factor but also a precursor to ductal carcinoma in situ and invasive cancer [3, 8]. The definition of atypia and the differentiation between hyperplasia, atypia and carcinoma in situ is very problematic. There is no strict definition of ADH and thus the judgment of the pathologist is often very subjective [6]. In our study we had cooperated with two pathologists well experienced in diseases of the breast. They both read the initial mamotomy and the surgical biopsy specimens. In our opinion this would assure a more accurate diagnosis of ADH.

In order to increase the oncological safety of diagnosing pathologies of the breast we recommend placing titanium clips in the area from which the mammotomic specimens are obtained, in case the patient requires any further diagnosis [9]. A marker allows to assure the surgeon and the radiologist that in the course of the subse-

quent open biopsy the appropriate specimen is obtained [10].

Stereotactic and ultasound-guided vacuum assisted biopsies are used worldwide for the diagnosis of breast lesions. The qualification criteria for stereotactic biopsy include clustered calcifications or mass distortion found in screening mammography. The ultrasound-guided technique is recommended for diagnosing small (10 mm or less) solid lesions, which are not well visualized on mammography scans, in patients with dense breast tissue or in pregnant or breast-feeding women in whom mammography is not indicated. Breast specialist are discussing usefulness of vacuum-assisted biopsy in patients with widespread microcalcifications and with multifocal lesions.

In the course of the study we had to tackle a very difficult issue. We had not realized how problematic it would be to convince a patient determined to undergo a minimal surgical procedure, such as a mammotomic biopsy, to undergo subsequent surgery when necessary. In the analyzed group of women almost half of the patients with ADH refused an open surgical biopsy after mammotomy. We believe this may have been brought on by a low level of awareness as to the possible consequences of neglecting the treatment of proliferative lesions, such atypical hyperplasia.

We agree with the opinion that the incidence of ADH is lower in the case of solid lesions, as compared to microcalcifications [3, 11]. In our study we had observed ADH in 5% of patients who had undergone stereotactic biopsy and only in 2% of patients who had undergone ultrasound-guided biopsies. We are convinced that mammotomic biopsy may, in many cases, be insufficient for the diagnosis of breast lesions. Although in the course of the mammotomic biopsy we can obtain more tissue than in the course of a fine needle aspiration biopsy, yet this amount is still inadequate to estimate the extension of the proliferative process and the tumor-free margins.

New concepts have appeared in the literature suggesting the methods of improving the diagnostics of ADH, however they are still experimental [12-14]. In the future, the use of monoclonal antibodies against purinergic receptors expressed on the surface of atypical and cancerous cells may help establishing correct diagnosis and choosing optimal surgical treatment [15, 16].

Although a mammotomic biopsy is more cost effective than a surgical biopsy after needle localization yet in some cases open biopsy is a necessity. In cases like those analyzed in our study an open biopsy is obligatory for a number of reasons, especially because atypical hyperplasia is a confirmed important risk factor of breast cancer and because in view of any suspicion the presence of a proliferative process treatment must be aggressive and radical. While reviewing literature we have come across a very important question to which we have also failed to provide an answer, what should be done in the case of patients with atypical hyperplasia in the initial mammotomic biopsy confirmed by the presence of atypia in the open surgical biopsy specimen. It is very difficult to state how aggressively such patients should be treated.

The diagnosis and treatment of atypical hyperplasia of the mammary gland is still controversial. Basing upon our own experiences and current literature data we would recommend performing open surgical biopsy in patients with atypical hyperplasia in the mammotomic biopsy specimen. Such patients should be clearly informed as to the high risk of developing breast malignancy and ought to be regularly monitored in a breast disease center.

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