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Signet Ring Cell Carcinoma of the Female Breast: Report of 3 Cases

Memenin Taşlı Yüzük Hücreli Karsinomu: 3 Olgu Sunumu

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Summary: Signet ring cell carcinomas of the breast have been described recently as an aggressive subtype of breast cancer. Three cases of signet ring cell carcinoma of the breast are presented, two of them diagnosed by biopsies, and one by cytology. Both of the biopsied cases were invasive lobuler carcinomas with more than 20% signet ring cell component,and with less than 25% insitu ductal component. Histopathologic properties of the signet ring cell carcinoma is presented in the view of the current literature. We aimed to attract attention to the importance of this aggressive form of breast cancer and being aware of its worse prognosis than classical lobuler carcinoma.

Key Words: Breast neoplasms, signet ring cell carcinoma, prognosis.

Özet: *Memenin taşlı yüzük hücreli karsinomu meme kanserleri içerisinde agresif seyirli bir altgruptur. Bu çalışmada iki tanesi biyopsi ile bir tanesi ise sitolojik olarak tanı konmuş olan üç adet memede taşlı yüzük hücreli karsinoma olgusu sunulmaktadır.Biyopsi ile tanı alan olguların her ikisi de %20'den fazla taşlı yüzük hücresi komponentine sahip olan invaziv lobuler karsinoma olguları olup %25'ten az insitu duktal komponent içermektedirler. Taşlı yüzük hücreli karsinomanın histopatolojik özellikleri bu konudaki son literatür gözden geçirilerek sunulmuştur. Çalışmanın amacı meme kanserlerinin bu agresif formuna dikkat çekmek ve klasik lobuler karsinomaya göre çok daha kötü prognozlu olduğunu vurgulamaktır.*

Anahtar Sözcükler: *Meme tümörleri,taşlı yüzük hücreli karsinoma, prognoz*

Signet ring cell (SRC) carcinoma of the breast represents a distinct subgroup of breast cancer with characteristic pathologic and clinical features. Pathologically, this tumor shows the characteristic histologic hallmark-the signet ring cell. We define as SRC carcinomas of the breast those lesions that show diffuse infiltration of stroma by individual epithelial cells characterized by a basophilic or clear cytoplasm containing mucin and a cresenting nucleus displaced toward one end of the cell. These cells had to be easily recognizable and comprised at least 20% of the tumor mass (1,2).

Mucin producing signet ring cells have been described in ductal and lobular carcinomas of the breast and in some instances were prominent cell type, prompting a designation of SRC carcinoma. In most reported cases and series of SRC carcinomas, patients with these tumors had a poor prognosis, with a high likelihood of metastatic disease, although the exact definition and classification of SRC carcinoma varied among authors (1-4). There has also been controversy as to whether SRC carcinomas were variants of lobular or ductal carcinoma or both. The cases reported by both Steinbrecher and Silverberg (2), and Merino and Livolsi (1) were histologically and ultrastructurally classified as lobular carcinomas. Alternatively, Hull et al(4) concluded that SRC carcinomas may be variants of ductal or lobular carcinoma. Mammary carcinoma displaying extensive collections of intracellular

mucin, in the form of SRCs, are in large part ignored by present classifications.

Several recent studies have disclosed conflicting results regarding clinical and histogenetic characteristics of SRC breast cancers.In the present report three cases of breast carcinoma containing numerous signet ring cells, diagnosed in the Pathology Department of Uludag University Medical School, between 1997 and 1998 are described, and the current literature on this subject is revieved.

Case Reports

Case 1: A 63 year old, white female (B-9732/98) presented to her physician's office with a >3 cm right breast mass that she had noted on self examination. The patient was treated with lumpectomy. The lumpectomy specimen from case 1 revealed on cut section a firm grayish tan mass that measured 3.5x2.5x2 cm. The mass had an illdefined margin. Histologically the tumor nodule consisted of of SRCs.There was also an infiltrating lobular carcinoma (ILC) pattern, and <25% insitu ductal carcinoma of micropapillary comedo and cribriform type (Figure 1). More than 20% of the infiltrative component of the tumor were signet ring cell type (Figure 2). There was also <25% apocrine differentiation in the tumor cells and the tumor contained areas of pleomorphic lobular carcinoma pattern. Lenfatic invasion was identified. Non-neoplastic breast tissue contained apocrine metaplasia and cystic changes. Cytoplasm of the signet ring cells contained musicarminophilic (Figure 3), PAS (+)-diastase resistant and Alcien blue (pH 2.5) positive material.

Case 2: A 63 year old white female (B-9953/98) presented to her physician with a large left breast mass noted during her routine controls for carcinoma of the colon operated two years ago. The carcinoma of the colon was adenocarcinoma with mucinous component, and the mucine material was extracellulary.The patient underwent biopsy and subsequent lumpectomy. The lumpectomy specimen from Case 2 revealed on cut section a firm, grayish tan mass that measured 5x4x3 cm. The mass had an illdefined margin. Histologic examination of the tumor nodule revealed SRC carcinoma with invasive lobular (Figure 4) and <25% in situ ductal carcinoma pattern Cytoplasm of the tumor cells were Mucicarmen and Alcien blue (pH 2.5) positive (Figure 5). No vascular invasion was identified. More than 20% of the infiltrative component of the tumor were signet ring cell type. Nonneoplastic mammary tissue contained areas of fibrosis, ductal hyperplasia without atypia and ductal ectasia.

Case 3: A 72 year old female (S-1356/97) presented with a right breast mass, concomitant with a cranial mass. Fine needle aspiration biopsy was performed for diagnostic purposes, and the mass in the brain was thoght to be a metastatic tumor from the breast. A biopsy was performed also from the mass in the brain in order to exclude a primary. Following the biopsy from the cranial mass, the patient expired in one month of time. The histologic examination of the biopsy from the cranial mass of the case 3 revealed Glioblastoma Multiforme, and the case was considered inoperable for both breast and cranial neoplasms. The fine needle aspiration biopsy from case 3 contained occasional loose sheets of malignant cells and many single, intact, disassociated cells. The neoplastic cells were round shaped, had a nucleus with a reticular type chromatine, and many of them were SRC type (Figure 6).

Laboratory materials and methods

Fine needle aspiration was performed with a 22-gauge needle and smears prepared by the pull-apart method. The slides were air dried, and stained with May Grünwald Giemsa method. Tissue from lumpectomy specimens was parafin embedded. In addition to hematoxylene-eosin, sections were stained with PAS with and without diastase digestion, mucicarmine,and alcien blue pH 2.5.

Discussion

SRC carcinomas of the breast have been separated recently as an aggressive subtype of breast cancer, distinct from mucinous (colloid) carcinomas.In 1976, Steinbrecher and Silverberg reported five new cases of SRC and found that these tumors demonstrated aggressive clinical behaviour and formed a pathologically distinct group (2).

SRC carcinoma of the breast, defined as a neoplasm composed in significant part (20% or more) of vacuolated mucicarminophilic cells, represents a distinct breast tumor with unusual clinicopathologic features. From their studies of mucin types and distribution, associated carcinoma, and ultrastructural examination, Merino and Livolsy conclude that SRC cancers are related histogenetically to lobular rather than ductal cells. Clinically, the SRC cancer behaves as an aggressive tumor which should be differentiated from mucinous (colloid) carcinoma. These tumors demonstrate an unusual metastatic pattern

with a propensity to involve serosal surfaces, gastrointestinal and urinary tracts; these metastases evoke a pronounced desmoplastic response leading to intestinal or urinary obstruction (1).

Steinbrecher and Silverberg counted any neoplastic cell containing a well deliniated cytoplasmic inclusion staining positively with mucicarmine as an SRC; distortion of the nucleus into a cresent shape was not a prerequisite for their diagnosis (2). Their series displays SRCs in 20 of 28 breast cancers examined (71%), and their data showed that many breast carcinomas, irrespective of histologic type, contained SRCs, they were uniformly present in relatively small numbers. But the majority of the tumors examined contained less than one SRC per High Power Field (HPF), and none of 28 averaged more than five per HPF. This is in contrast to the five cases comprising their report, in which the number of SRC/HPF ranged from 18 to 36. Histologic data presented in their study suggest that the five tumors presented are cases of ILC of the breast displaying prominent SRCs.

Frost et al concludes that breast carcinomas with SRCs represent a heterogeneous group and, regardless of the histologic type, a prominent SRC component connotes a more aggressive carcinoma. In their series of 99 infiltrating lobular carcinomas, they concluded that the presence of 10% or more SRCs represents a poor individual prognostic factor in stage I ILCs (3). They recommend against defining an entitiy of SRC carcinoma.Instead, the presence of SRCs should be reported as one of several prognostic variables identified in ILCs.It has not yet been determined whether SRCs in infiltrating duct carcinomas have a similar prognostic significance (3).

Differences have been reported in the age distributions of the pure,or classical, and the variant forms of ILC (5). DiCostanzo and coworkers found that patients with classical ILC tended to be younger than those with variant types of invasive lobular carcinoma (6). A major problem in attempts to define and compare the so-called variant forms of ILC has been the rarity of this entire group of tumors and the relatively small numbers of the several variant lesions. A series of 230 patients with stage I and II ILC included 176 women with classical lesions and 54 (23%) with variant growth patterns (6).

Classical ILC consists of small, uniform cells with round nuclei and inconspicious nucleoli (5). A variable proportion of cells have intracytoplasmic lumina containing sialomucins demonstrable with the mucicarmine and Alcien blue stains (7,8). When the secretion is prominent, the cells have a SRC configuration. With the aforementioned stains, it is often possible to demonstrate small amounts of secretion in many non-SRCs. In one study of ILCs, at least 10% of the cells in 45% of the tumors had SRC features when studied in routine histological sections (3). The majority of so called SRC carcinomas are forms of ILC (1,2,6-8), but similar cells are also found in invasive duct carcinomas (4,9).

Some ILCs consist entirely or in part of cells with relatively abundant, eosinophilic cytoplasm. The nucleus in these cells tends to be hyperchromatic and eccentric, sometimes creating a plasmocytoid appearance (5). These cells have been referred to variously as myoid (6), histiocytoid (10,11), and pleomorphic lobular carcinoma (12,15). Eusebi et al. emphasized the presence of apocrine differentiation in pleomorphic invasive lobular carcinoma and concluded that these patients have an especially aggressive clinical course because 9 of 10 patients in their series developed recurrences (12). Each of these nine patients had nodal metastases at the time of diagnosis. Pleomorphic lobular carcinoma of the breast is a subtype of lobular carcinoma of the breast that is well recognized in the surgical pathology literature. Fine needle aspiration recognition of this subtype is important, for the subtype characteristically pursues an aggressive clinical course as compared to the classical lobular carcinoma of the breast. Dabbs et al. propose classifying these tumors as a high (poor) nuclear grade variant of lobular carcinoma, analogous to the grading scheme in use for aggressive ductal carcinomas (15). One of our cases showed areas of pleomorphic lobular carcinoma and apocrine differentiation.

Most studies seem to indicate that patients with classical ILC have a better prognosis than those with variant forms as a group, but the differences have not been statistically significant. No reproducible differences in prognosis have been demonstrated among patients with different variant lesions, and it is evident that very large numbers of cases will be needed to document significant differences if they exist. Consequently, no distinction should be made between classical and variant forms of invasive carcinoma with regard to therapy.

In conclusion, SRC carcinoma of the breast is an aggressive form of the lobular or ductal carcinoma, and whether the accompanying pattern is lobular or ductal, the prognosis gets worse with the presence of SRCs, and the pathologist must be aware of their presence in order to alert the clinician for strict follow up of the patient.

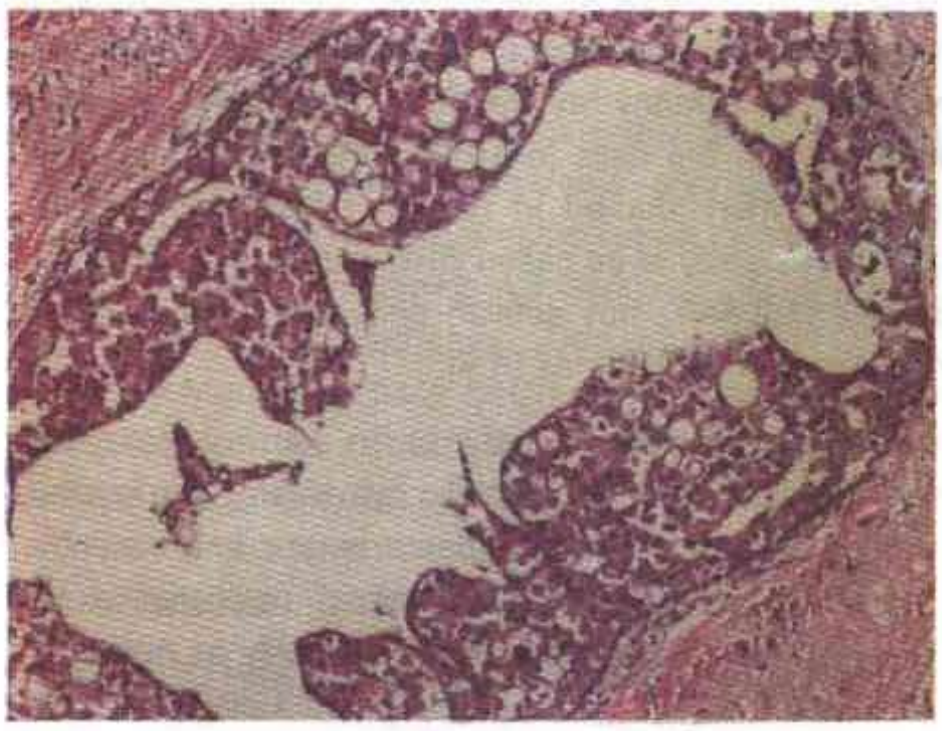

Fig. 1. In situ ductal component of case 1 (B-9732/98 HE x100).

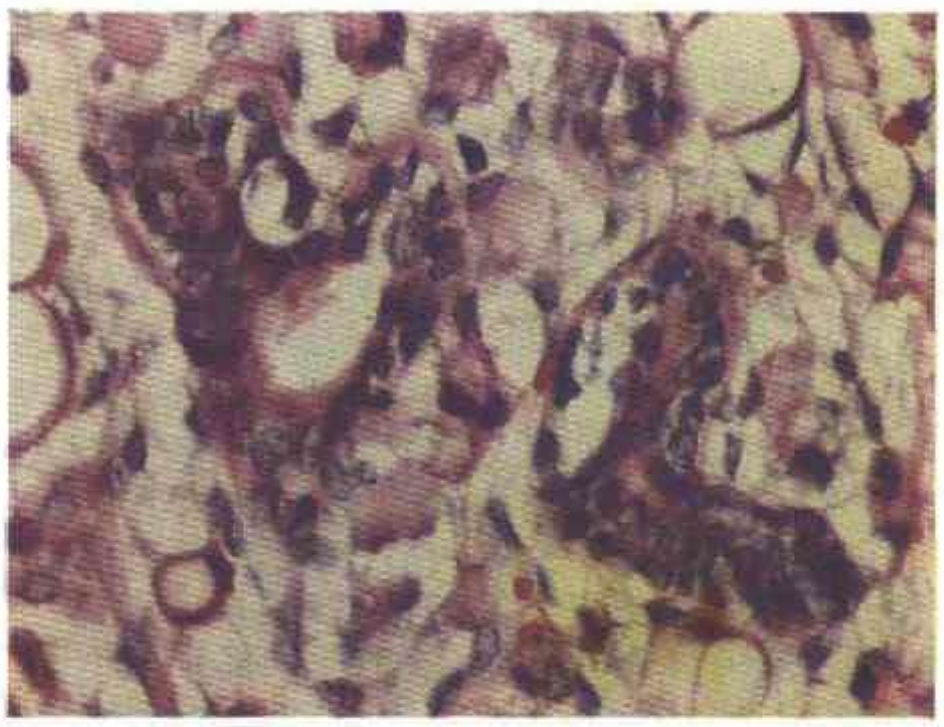

Fig. 2. Signet ring cells diffusely dispersed in stroma in case 1 (B-9732/98 (HE x400).

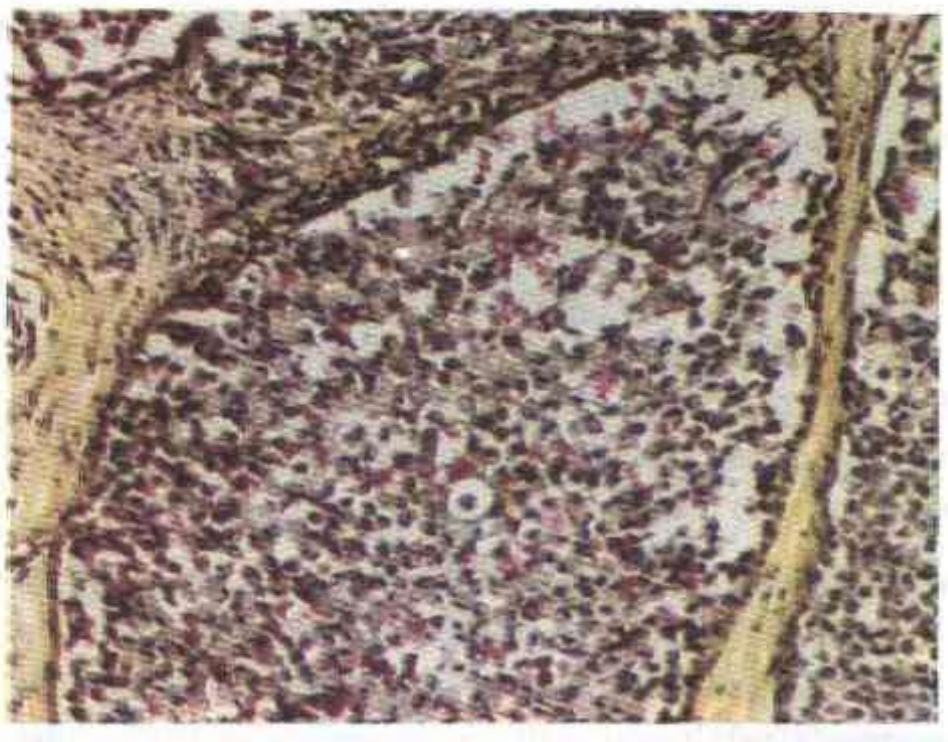

Fig. 3. Musicarminophilic signet ring cells in situ ductal carcinoma, (B-9732/98 musicarmen x400).

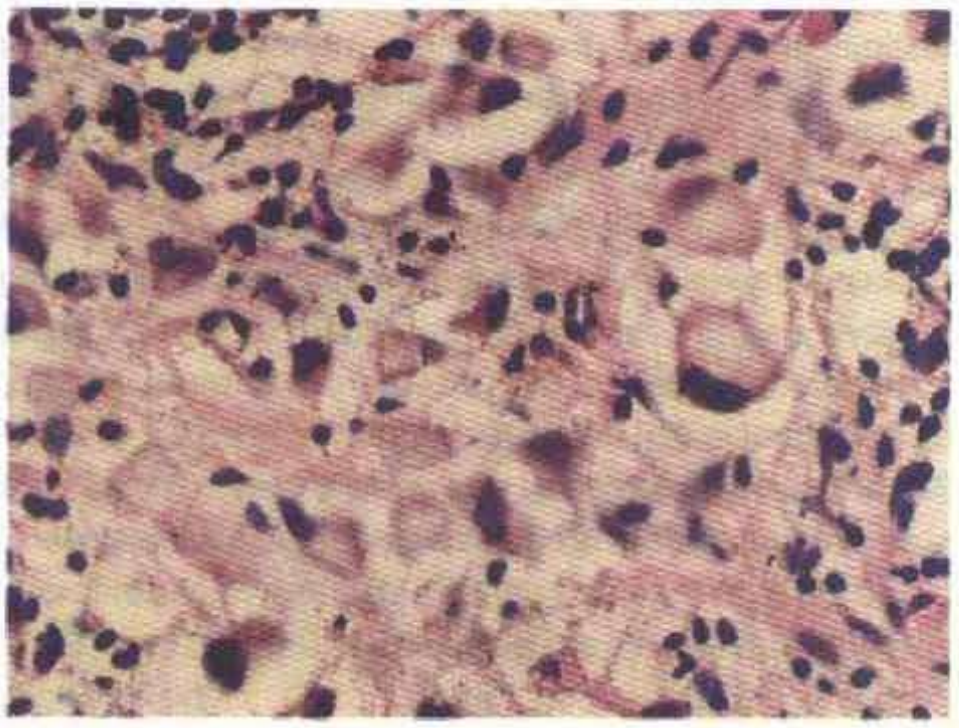

Fig. 4. Signet ring cells in invasive lobuler component of case 2 (B-9953/98 HE x400).

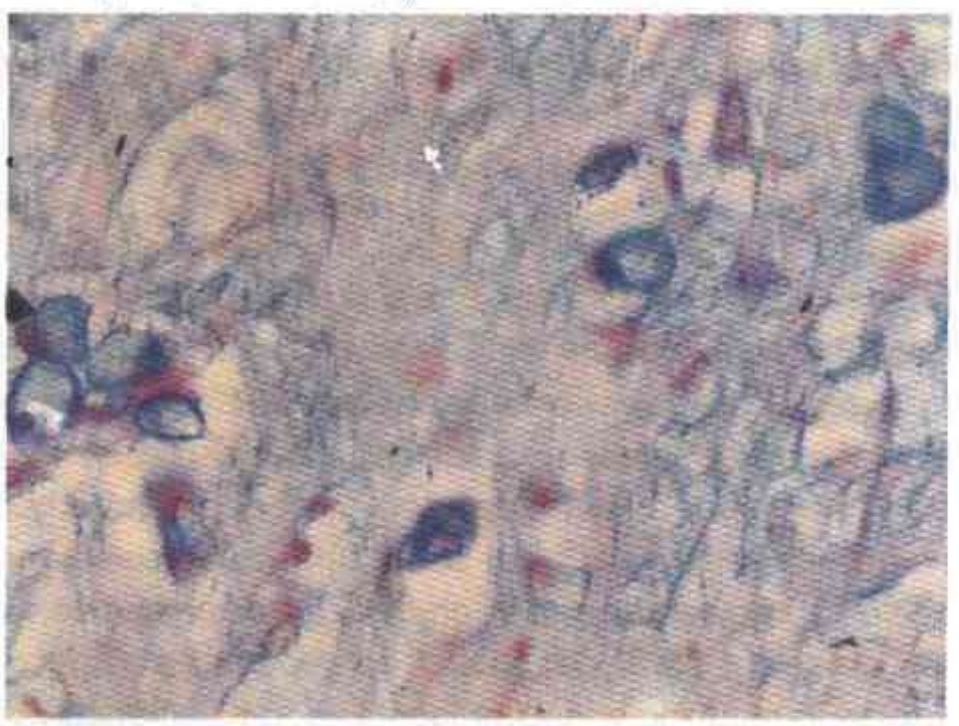

Fig. 5. Cytoplasmic alcian blue positive material (B-9953/98 Alcian blue x400).

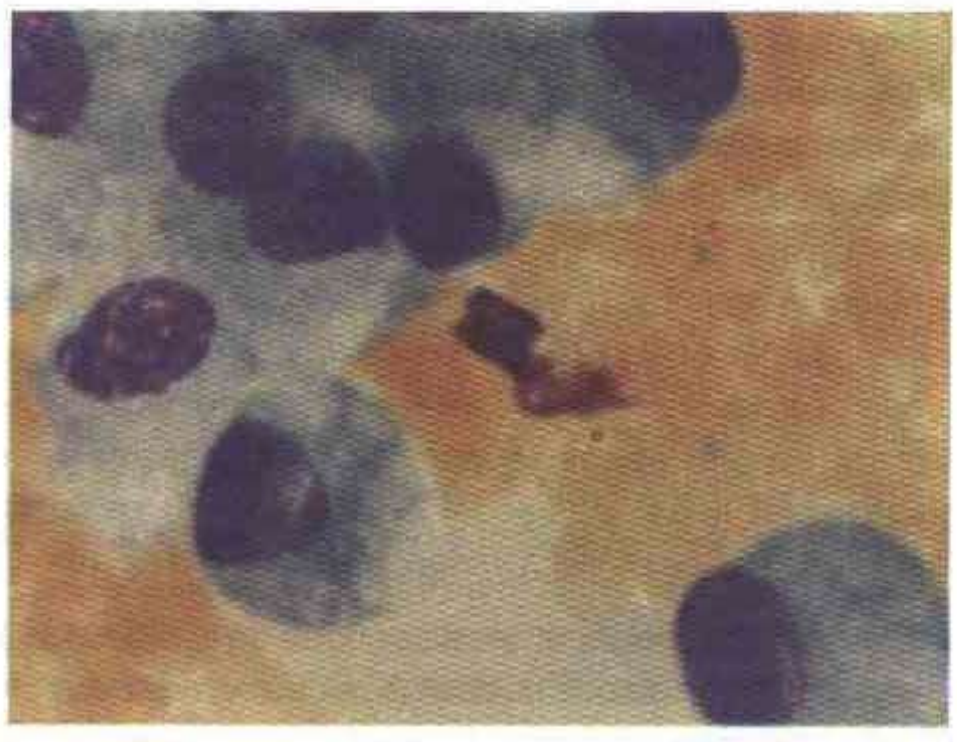

Fig. 6. signet ring cells in case 3 (S-1356/97 MGG x1000).

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