Letters to the editor

Gastrointestinal metastases in lobular breast cancer

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In a previous issue of *Annals of Oncology*, Bamias et al. reported the clinical case of a patient with rectal metastasis from lobular carcinoma of the breast (ILC) [1]. In their summary of the literature, our series of 17 patients with colorectal metastases reported in 1992 is mentioned [2]. However, five of the seven patients with rectal localisation selected for their table, suffered from additional infiltration of parts of the colon. In only two cases the rectum was the sole localisation of metastatic gastrointestinal involvement. We would like to add some more information on this subject to put it into perspective.

One patient (50 years) developed diarrhoea caused by rectal stenosis 15 months after the diagnosis of locally advanced, lobular breast cancer. Endocrine treatment resulted in local response until death due to cerebral metastases 22 months later.

The second patient (51 years) had diarrhoea and weight loss due to severe rectal obstruction, seven years after the treatment of ILC . Anthracyclin based chemotherapy resulted in a fair response of 9 months without the need for a colostomy. She eventually died 11 months after the diagnosis of rectal involvement due to diffuse peritoneal metastases.

Solitary rectal metastasis of breast cancer is a rare condition. In contrast, gastric involvement is a more common event, also prefentially occurring in ILC [3]. In our series 36 of 51 patients with gastric metastases had ILC [4]. Endoscopy showed mainly a diffuse linitis plastica-like infiltration (57%), but also localised lesions (18%) such as ulceration and a polypoid mass, or stenosis due to extrinsic compression at the cardiac junction or the pylorus (25%) were present. Symptoms were non-specific: anorexia (71%), epigastric pain (53%) and vomiting (41%). The interval between primary breast cancer and intestinal complaints was prolonged (median 62 months, range 2–104). Metastases at other sites were present in 48 of 51 patients. The presenting site of metastatic disease was: skeleton (43%), stomach (27%), lung (8%) and liver (4%). The overall response to systemic therapy was fairly good with 46% despite the pre-treatment in half of the patients. Calculated from the detection of gastric metastases the median survival was 11 months with some long-term survivors leading to a two-year survival of 23%.

Based on tumour invasion primarily in the subserosa, it not surprising that the endoscopic biopsies might be negative. In our series of gastric metastases endoscopic biopsies were positive in 35 patients; in six cases a second endoscopy revealed tumour cells, while in 10 patients with a negative histology the diagnosis was based on circumstantial evidence from the characteristic endoscopic features along with metastases at other sites. Also, in the case of Bamias et al. repeated biopsies were helpful [1].

In conclusion: especially in lobular type of breast cancer metastases in the gastrointestinal tract occur, often with metastases at other sites as the skeleton. Gastric metastases occur more frequently than colorectal metastases.

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Detection of tyrosinase mRNA in tumor tissue microdissections from classic Kaposi's sarcoma

Classic Kaposi's sarcoma (CKS) is a systemic, multifocal, angiomatous, rare tumor [1]. CKS is more common in the Mediterranean area (mostly, in people of Italian and Greek origin), with the highest incidence found among Jews in Israel [2]. Although Kaposi's sarcoma-associated herpesvirus (KSHV or human herpesvirus 8) has been causally linked to CKS, the factors involved in the tumorigenesis and prognosis of the disease are still unidentified [1]. In addition, very little is known about the molecular mechanisms underlying the prevalence of clinical and pathological correlation between CKS and malignant melanoma (MM) [2]. In our previous study, circulating melanoma-associated (MA) markers were detected in peripheral blood of CKS patients by reverse transcriptase-polymerase chain reaction (RT-PCR) [3]. Briefly, 13 (62%) out of 21 CKS patients were found positive to at least one of the two most specific MA markers used in that study [in particular, 3 of 21 (14%) and 11 of 21 (52%) were found positive to tyrosinase and MelanA/Martl markers, respectively] [3]. To evaluate whether presence of MA markers in peripheral blood of CKS patients could be due to abnormal expression of such mRNAs in CKS tumor cells, we performed a RT-PCR analysis on a subset of microdissected tumor tissues from CKS patients.

Histological samples were selected from 16 patients with ascertained diagnosis of CKS (archival stained slides were further evaluated in order to confirm previous diagnosis and better define the specific histological type). Serial 4-μm sections were cut from formalin-fixed, paraffin-embedded-tissues and slides were stained with methyl green before laser capture microdissection using a PixCell laser capture microscope (Arcturus Engineering, Mountain View, California) as previously described [4]. Total cellular RNA was isolated and subsequently amplified by RT-PCR with primers specific for

tyrosinase and MelanA/Mart1 markers following our reported experimental protocols [5].

Amplification of GAPDH mRNA (a housekeeping gene product as positive control) gave no PCR product in six tumor samples of our series. Figure 1 shows RT-PCR results in the remaining 10 CKS tissues with expression of GAPDH mRNA. Specific amplification for individual MA markers was only observed for tyrosinase in cases 2, 10, and 12 of our series (as also confirmed by Southern blot hybridization) (Figure 1). For eight of such patients (cases 2, 3, 7, 9, 10, 12, 14, and 15 of Figure 1), peripheral blood sample was obtained (after a written informed consent) and RT-PCR was performed. Tyrosinase was detected in one CKS patient (case 2; 12.5%), whereas MelanA/Mart1 marker was found in three blood samples (cases 3, 7, and 9; 37.5%) (data not shown).

Considering the RT-PCR results on microdissected tumor tissues, detection of tyrosinase in 3 of 10 (30%) samples and absence of amplification for MelanA/Mart1 is a strong indication that these two markers present a different specificity as melanoma-associated antigens. However, we found expression of both MA mRNAs in peripheral blood of CKS patients (at rates comparable to those we have previously reported [3]). While positivity to tyrosinase in peripheral blood from CKS patients seems to be due to the presence of metastatic tumor cells expressing this MA marker, there is no explanation for the detection of circulating MelanA/Mart1. One could speculate that in CKS patients cells of melanocytic lineage expressing MelanA/Mart1 might be somehow induced to dissemination and, thus, found in peripheral blood. Further improvements of bio-technologies are awaited to systematically perform additional studies on large collections of CKS tumor tissues in order to confirm our findings.

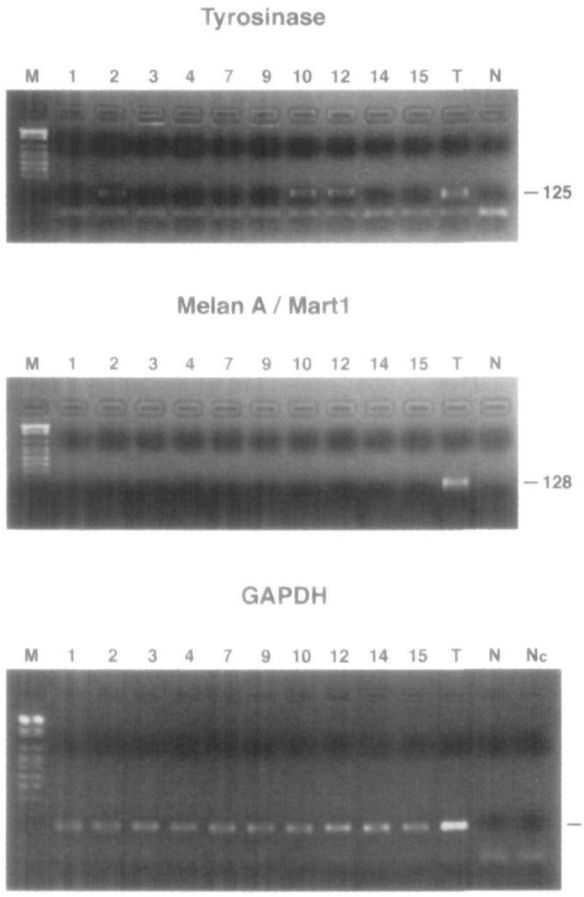

Figure 1 RT-PCR results on microdissected tumor samples from CKS patients. PCR products were separated by electrophoresis on a 2% agarose gel and directly visualized by ethidium bromide staining. T – human melanoma-derived cell line SK-MEL-29 as positive control, N – PCR reagents and primers without RNA as reaction negative control, Nc – RT reagents and random examers without RNA as cDNA negative control; M – marker.

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