Usefulness of Breast MRI in a Patient with Genetic Risk

L. Cortesi[1], B. Canossi[2], M. De Santis[2], P. Panizza[5], G. Rossi[3], D. Turchetti[1], A. Del Maschio[6], S. Ferrari[4], R. Romagnoli[2], M. Federico[1], V. Silingardi[1]

Dipartimento di Oncologia ed Ematologia[1], Cattedra e Divisione di Oncologia Medica, Dipartimento di Diagnostica per Immagini[2], Dipartimento di Scienze Morfologiche e Medico Legali[3], Sezione di Anatomia Patologica, Dipartimento di Scienze Biomediche[4], Sezione di Chimica Biologica; Università di Modena e Reggio Emilia, Modena. Dipartimento di Radiologia[5], Istituto Scientifico Ospedale S.Raffaele; Istituto di Radiologia[6],Università Vita-Salute San Raffaele; Milano, Italy

We describe an interesting case-report represented by a patient carrying BRCA1 mutation, recruited for the study "Multicenter evaluation of Magnetic Resonance Imaging (MRI) in early diagnosis and prevention of breast cancer in high risk population", diagnosed with breast cancer on the basis of MRI findings but not with conventional mammography and ultrasound (US). She was already affected at 53 years of age by a multifocal Ductal Infiltrating Carcinoma (DIC) in the left breast; then, she had an axillary and sovraclavear nodal recurrence of the disease, three years after the initial diagnosis. Since other relatives were affected by breast cancer (mother, sister and niece) and two arose at early age (<40 years), BRCA1 mutational analysis was offered to the patient, identifying a nonsense mutation on the exon 13. Furthermore, this patient was recruited to study contralateral breast and at the second round, two little foci, suspicious of malignancy, were identified only with MRI, but not with mammography and ultrasonography. The final diagnosis was multifocal Ductal Carcinoma in situ (DCIS); the major focus measured 3 mm. In our patient MRI has shown a major sensitivity with respect to conventional radiology and US and has provided a very early diagnosis in this woman at genetic risk.

Key Words: BRCA1, Breast, MRI

About 5%-10% of all breast cancer cases are associated with or due to a patient's genetic predisposition to the disease; a genetic predisposition accounts for at least 9,100 new breast cancer cases in the United States per year (1). Breast and ovarian cancer susceptibility genes identified thus far, BRCA1(2) and BRCA2 (3), account for about 50% of the genetically induced breast cancer cases; for the remaining cases, other, still undefined, BRCA genes are suspected (4-6). The lifetime risk of eventually developing breast cancer accumulates to 36%-85% and 25%-60% for carriers of BRCA1 and BRCA2 mutations, respectively. Moreover, if a gene carrier has already experienced breast cancer, she faces a 60% risk of developing a second breast or ovarian cancer (7). An important feature of familial breast cancer is the patient's age at diagnosis. As opposed to women with sporadic breast cancer, women with a BRCA mutation develop breast cancer at a significantly younger age and, accordingly, more often in the premenopausal period. By the age of 50, more than 50% of the BRCA1 or BRCA2 mutation carriers have already developed the disease (8,9). Accordingly, the current recommendations for breast cancer screening may not be sufficient for gene carriers. Because of the high risk of developing breast cancer and the early onset of the disease, close screening examinations of proved or suspected gene carriers should start at a substantially earlier age than is recommended for the general population. However, the sensitivity of mammography decreases when breast tissue is dense and this is seen in 40-50% of women under the age of 50. On the other hand, the sensitivity of contrast enhanced dynamic breast MRI is not modified in dense tissue. Furthermore, defects in double-strand break repair or in any of the DNA repair processes caused by genetic mutations can be accelerated by conventional radiology. In October 2000 a multicenter study on the evaluation of MRI in early diagnosis and prevention of breast cancer in high risk population, aimed at assessing the usefulness of a MRI screening of breast cancer in carriers of BRCA1, BRCA2 and p53 started sponsored by the Italian Istituto

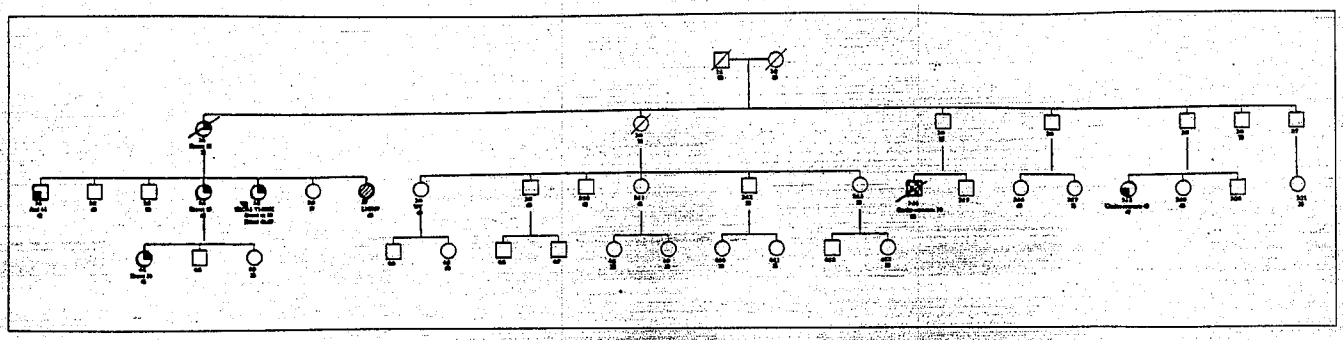

Fig. 1 - Pedigree of the patient found positive at breast MRI. The patient is indicated by an arrow. Four breast cancers (one bilateral) and four different types of tumors (anus, non-hodgkin's, uterine sarcoma and gastric sarcoma) are shown.

Superiore di Sanità. Here we describe a patient carrying BRCA1 mutation, diagnosed with breast cancer on the basis of MRI findings but not with conventional mammography and ultrasound.

Study Population

Since 1996, at the Oncology Division of Modena and Reggio Emilia University, 337 patients were investigated for BRCA1 and BRCA2 analysis by direct automated sequencing (DAS). Out of these cases, 283 were analysed for BRCA1 gene and 54 for BRCA2 gene. 56 individuals resulted carriers of a pathogenetic mutation in BRCA genes (50 BRCA1 and 6 BRCA2). So far 20 BRCA1 and 2 BRCA2 carriers were recruited into the study. Five women were already affected by monolateral breast cancer and three by ovarian cancer

Case Report

In 1996, a patient affected at 53 years of age by multifocal ductal infiltrating carcinoma (DIC) characterized by grading III with prominent lymphoid stroma, negative hormonal receptors, high proliferative rate and with the involvement of one axillary node, was interviewed in order to obtain, through a detailed questionnary, extensive genealogic and medical information. At this time the patient had had a recurrence of the disease, three years after the initial diagnosis. The patient's pedigree of four generations was drawn. Forty-three individuals were investigated, arising from two parents dead without tumors (first generation), and further distributed in three generations, with a high global incidence of different types of tumors (anus, non-Hodgkin's lymphoma, uterine sarcoma and gastric sarcoma) and, moreover, four female breast cancers. Two breast cancers arose at less than 40 years of age (Fig.1).

The index case of the above described family underwent BRCA1 mutational analysis and a novel nonsense mutation at 4406 nucleotide which caused a stop at 1428 amino acid was found (Fig.2).

In 2000 she was recruited for the research project on "multicenter evaluation of MRI in early diagnosis and prevention of breast cancer in high risk population".

BRCA1 mutational analysis. Blood sample, for genomic DNA extraction, was collected from the patient after her informed consent.

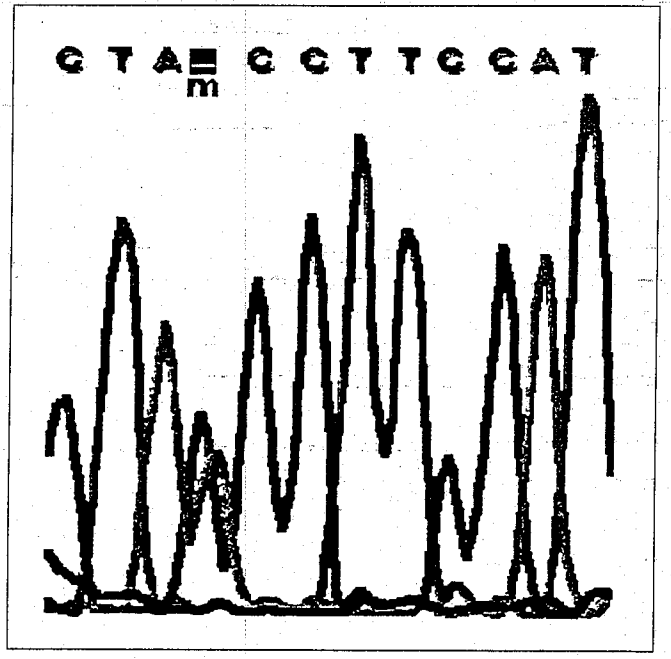

Fig. 2 - Detection of a novel BRCA 1 mutation, 4406C>A on exon 13.

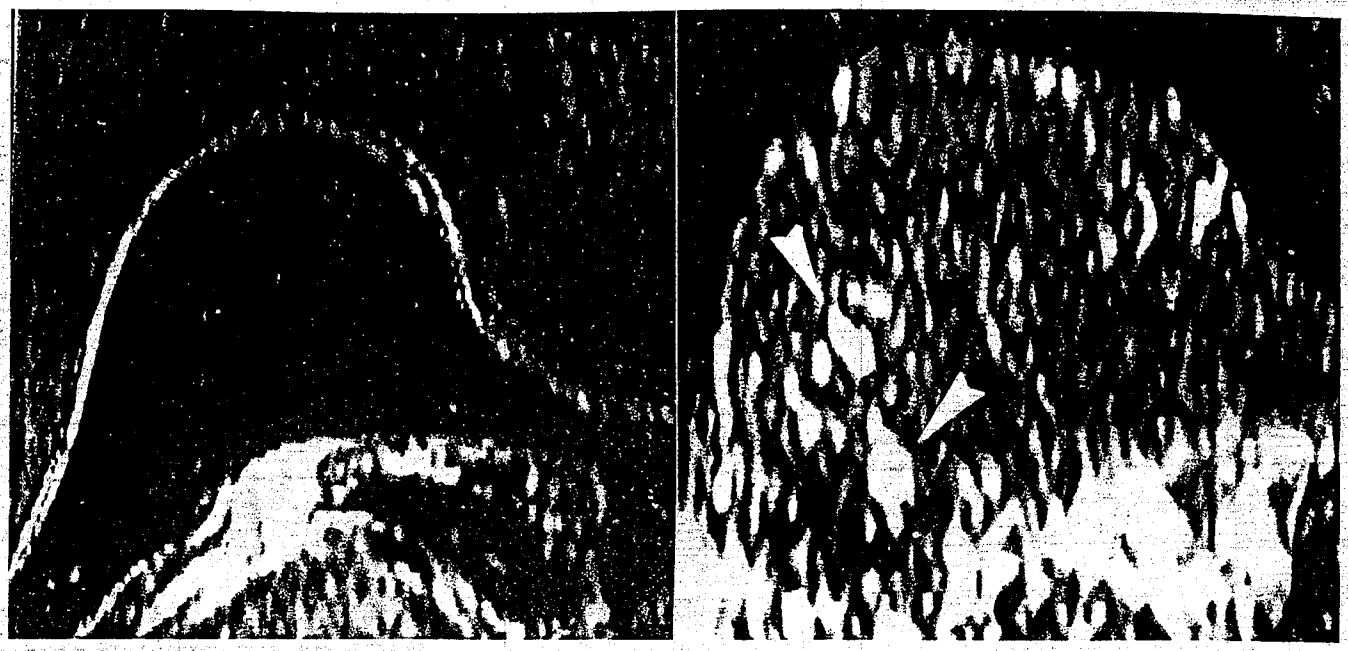

Fig. 3 - A) Breast MR image of the 2000 year: the exam is negative for breast cancer. B) Breast MR image of the 2001 year: multiplanar reconstruction, after subtraction, of the axial plane. The two tumor foci are clearly depicted (arrows).

For BRCA1 analysis, we choose to study the most frequently mutated exons. Furthermore, when an alteration was identified in an index case, only this mutation analysis was performed. For BRCA1 analysis we used 17 primer pairs, as described by Friedman et al. (10), to amplify exons 2,3,5,6,8,11,13,16,17,18,19 and 20. The purified template was sequenced using ABI PRISM BigDye Terminators Cycle sequencing Kit (Applied Biosystem, USA) and analyzed on ABI 377 sequencer (Applied Biosystem, USA). Sequence comparison was carried out using the Autoassembler programme (Applied Biosystem, USA) and Dnasis (Pharmacia, USA).

MRI, US and mammography. The patient was examined every year and on the same day she underwent physical exam, US, mammography and MRI. Mammography was always performed in double projection, medio-lateral and cranio-caudal and when necessary was completed with oblique and detail projections. US was performed with linear probe small-parts (10-13 MHz). MRI was performed with a superconduttive 1.5 T magnet (SIGNA, GE, Milwaukee, USA) and dedicated bilateral coil. The patient had a history of previous left mastectomy, therefore only the right breast was examined. The sequences utilized were: axial fast spin-echo (FSE) fat sat (TR 4500; TE 112; ET 8; thk 4 mm); dynamic coronal 3D fat sat (TR 18.6; TE 1.9; FOV 18 cm; thk 2 mm; matrix 256 x 160; 1 scan; 64 slices; 1'48"); one pre-contrast sequence and five post-contrast series (Gd-DOTA 0.1 mmol/Kg). The images were postprocessed with digital substraction and multiplanar reconstructions (MPR) and maximum intensity projection (MIP). Analysis of kinetic of contrast uptake was performed in selected regions of interest according to the formula: (SI post-SI pre)/ (SI pre) x 100 (%).

Biopsy under MRI guidance. A dedicated stereotacttic devive to locate breast lesions was used with a 1.5 T MRI system (Intera; Philips Medical Systems). The device is unilateral and consists of a breast compression device with two compression plates. On both compression plates there are fixed marking tubes, which are visible on MR images as hyperintense markers to serve for the definition of stereotactic coordinates. The upper compression plate has small holes through which a needle can be inserted to reach the lesion. The patient lies in a semi-prone position, the breast compressed into the device. A circular surface coil is located between the patient and the breast compression device to improve the S/N. A fully MR imaging compatible 21-gauge needle is employed.

To localize lesions, 3D T1 FFE sequences (TR/TE: 9.2/4.5 ms; slice thickness: 2.0 mm/ no gap) are acquired in transverse plane. Looking at the vertical marking tubes the distance in feet-head direction is determined; looking

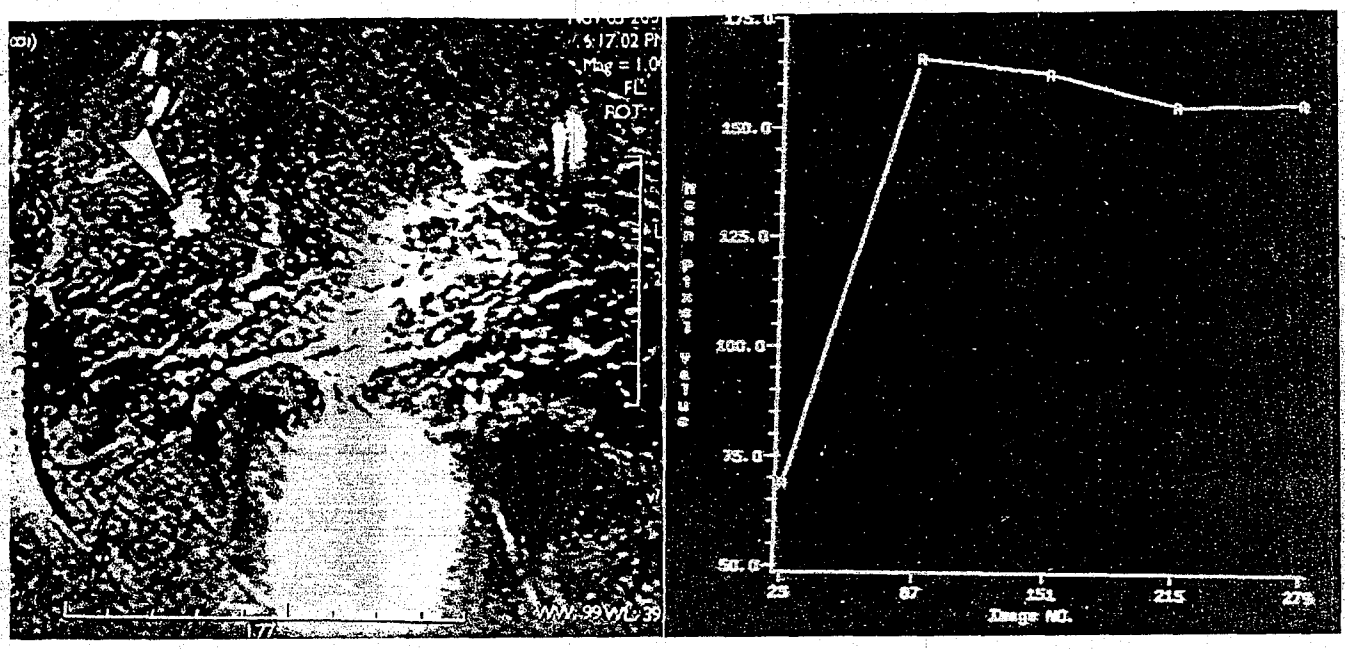

Fig. 4 - A) 3D MR coronal plane image after substruction: small area of focal enhancement (7 mm), with speculated borders, at right upper lateral quadrant (arrow). B) The time-intensity curve shows early contrast enhancement (about 100% at first minute) and slowly wash-out.

at the horizontal marking tubes the distance in antero-posterior direction is defined. In this way the compression plate hole inserts the needle into the lesion. The depth of needle insertion into the lesion is obtained by measuring the distance between the vertical tube and the lesion. After insertion, the position of the needle is controlled with turbo spin-echo (TSE) T1-weighted sequences (TR/TE: 204/20 ms; slice thickness, 2.0 mm/ no gap). In order to minimize the needle artefacts for needle visualization, TSE sequences are used.

Results

All the diagnostic examinations performed in the year 2000 were negative for breast cancer in the residual mammary gland (Fig.3A). In November 2001 the patient underwent a routine physical exam, mammography and US which were all negative for carcinoma. On the other hand, MRI pointed out two focal areas of intense contrast enhancement in the dynamic sequence with contrast paramagnetic medium. Both of them were localized deeply, at the upper lateral quadrant, and had spiculated borders; the larger one had a dimension of 7 mm, the smaller one had a diameter of 5 mm (Fig.3 B). The time-intensity curve of both lesions showed early contrast enhancement already in the first sequence, with enhancement above 100% in the first minute; the larger lesion showed a slow wash-out, while the smaller one had further enhancement at the third minute and reached a plateau during the following minutes. The first nodule had striking MRI features, suggestive of malignancy (Fig.4 A,B); the second nodule was suspicious, but in a not specific manner. So the patient was recalled for the second US look which confirmed again the impossibility to diagnose the carcinoma by this modality, in spite of careful sounding of the upper lateral quadrants. The mammoscintigraphy, performed on the bases of the national protocol, was negative too. The following step was biopsy under the guidance of MRI.

Before submitting the patient to MRI Stereotactic Fine Needle Aspiration, at S.Raffaele Hospital in Milan, she was examined once more, with mammography, sonography and contrast enhanced MRI. Mammography showed a completely fat breast, without suspicious images and sonography, guided on the basis of MR images, wasn't able to identify any lesion. MR confirmed two small lesions in the upper lateral quadrant of the right breast.

To confirm the diagnosis of malignancy, three fine needle aspirations and cytological samples were performed. The results were suspicious for malignancy on the basis of scattered atypical ductal cells with unlarged nude nuclei found at cytologic examination. Finally, the patient underwent mastectomy and multifocal, high grade DCIS were observed in all the mammary gland.

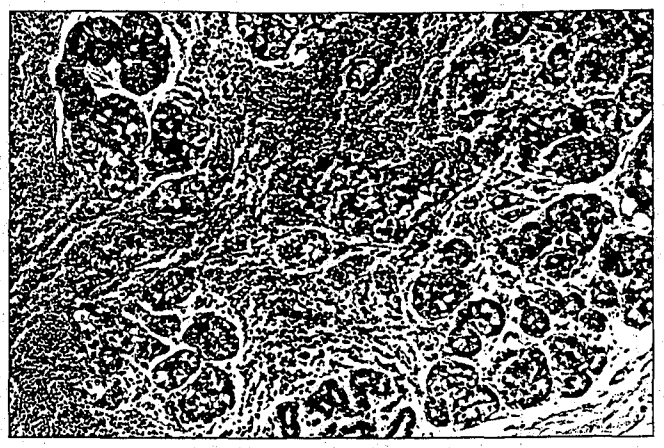

Fig. 5 - Multiple foci of DCIS with lymphoid stroma. Hematoxylin and eosin, high magnification X200.

The major focus measured 3 mm. (Fig V)

Discussion

The above mentioned case-report supports the usefulness of our multidisciplinary approach in the early diagnosis of breast cancer. In fact, an accurate genetic counselling that identifies an hereditary breast cancer according to our criteria (11), associated with an aggressive tumor phenotype (grading III, hormonal receptors <10%, high proliferative rate (12)) are able to identify individuals at very high risk for carrying a mutation on BRCA1 gene. Furthermore, an optimal analysis methodology, based on the DAS, which is considered the gold-standard DNA analysis, is necessary to identify all the genomic mutations. Finally, a patient found positive to genetic mutation should be investigated for an early diagnosis by the most sensitive technique i.e. breast MRI, associated to conventional radiological exams. Concerning invasive breast cancer, MRI is the most sensitive modality presently available for detection and staging. Sensitivity approaches the 100% margin. MR failures in detecting invasive breast cancer are related to technical drawback or are due to slow enhancing cancer (lobular) embedded into enhancing mastopathic alterations. Very rarely invasive breast cancer doesn't enhance at all. Concerning DCIS, MRI sensitivity and specificity are much lower than for invasive breast cancer. The enhancement in DCIS is seen in a fraction ranging from 70 to 80% and in 30-40% of the cases enhancement is not specific (13). Moreover, it seems that high grade DCIS enhances more frequently than low grade DCIS. In our case MRI has permitted to identify very small foci of high grade DCIS while mammography, which has, in women with predominantly fatty breasts, a sensitivity around 80%, was totally negative for tumor (14). It has to be pointed out that, in BRCA1 gene carriers, which have a mutated pathway in the DNA repair, breast MRI is safe concerning a possible radiological damage. Therefore, it seems appropriate to propose this methodology to the BRCA1 carriers. Finally, the patient has had a benefit in such an early diagnosis, since she didn't have to undergo chemotherapy and she has now an approximately 100% chance of cure.

After this event, the patient understood the importance of genetic testing and of an early diagnosis. So she informed many of her relatives on the opportunity of undergoing a BRCA1 mutational analysis test themselves, and they are now asking for this.

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Dr. Laura Cortesi
Azienda Policlinico Modena
Via del Pozzo 71,
41100 Modena, Italy
Tel.: +39-59-4224334; Fax: +39-59-4224152