

Inflammatory breast cancer



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Inflammatory breast cancer

The very original definition of carcinomatous mastitis suggests the main diagnostic difficulty of this onchologic condition. Actually it is more correctly appointed as inflammatory breast cancer, because notwithstanding the inflammatory appearance, it is a true systemic breast cancer, for which surgery represents an only marginal treatment resource. If is now well known that radical mastectomy is ineffective and only a combination of CT and RT offers survival results of some value. But the actual correct multi modal treatment cannot be undertaken if not after a correct diagnostic confirmation, avoiding an anti-inflammatory therapeutic attempt that is time consuming and possibly deceptive. Surgery and histology can be the only means of a correct diagnosis when FNAB is falsely negative, but the lymph nodes must be the preferential tissue to examine to avoid long lasting drainage from the breast parenchyma after a biopsy, that delays the beginning of the true treatment.

KEY WORDS: Breast, Breast cancer, Inflammatory cancer.

Introduction

"Carcinomatous mastitis" is an old denomination of a particular form of breast cancer, firstly described mainly in young women during pregnancy or during breast feeding, and with a clinical presentation similar to a "mastitis", so favouring an erroneous diagnosis with the most common evenience of an infection of the breast during those physiologic phases.

The resemblance with a flogistic disease of the breast is not complete, because not all the signs of flogosis are present at clinical presentation. Moreover the usual treatment of a mastitis of course is ineffective and also that usual for a breast cancer is very poor of long and short term positive results. The disease needs instead a complex strategy of multimodal therapy, and is the only form of breast cancer requiring an emergency treatment.

Volkman was the first to describe the disease in 1875 as "acute cancer" of the breast ¹, underlining the frequent bilaterality. The same denomination was still that of **Lee** and **Tannenbaum** in 1924 ². But in 1938 **Taylor**

and **Meyer** ¹ gave the now accepted the definition of "inflammatory cancer" of the breast (IBC), noting that not always a truly "acute cancer". in spite of its rapid onset and evolution, presents the same clinical patterns of an "inflammatory cancer".

Actually it is well known that IBC represents 1,3% - 4% of all breast cancer, not peculiar of pregnancy and breast feeling, more frequent at the age between 47 and 59 years, then earlier then the usual breast cancer age, but more frequently in women about menopause and very rarely also the male breast.

The incidence of IBC is however different in some countries, as in Belgium were the incidence is 2-3% of all breast cancer, usually at the age of climaterium. In U.S.A. it represents 6% of all new breast cancer. The higher incidence was described by **Mourali** in 1980 ³ among Maghreb women, ten times more frequently in the young ones and here generally related to pregnancy and lactation, with more possible confusion with the true mastitis.

It has been demonstrated by **Juret** in 1964 ⁴ that IBC can be also induced by incongruous estradiol treatment of the menopause.

Personal experience

We refer to four cases observed over a long period of

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time, which started well before that actual therapeutic schemes were defined.

The first case refers to a 56 years old nun, affected by the typical IBC since her first clinical presentation: swollen and painless left breast, pinkish color of the skin (Fig. 1), and very hard consistence to palpation. Notwithstanding a repetitive FNAB the suspected diagnosis was not confirmed, and also if the suspect of the true diagnosis was very high no oncologist then (1984) accepted to treat the patient with CT or RT, because of the lacking histological confirmation. Therefore a Halstead's mastectomy was performed that gave only the correct diagnosis of IBC. The patient was submitted to RT but, three months after surgery an exudative left pleural effusion opened the scene of the final life act for the patient, notwithstanding an adjunctive CT was instituted.

Two subsequent cases, respectively 58 and 67 years old observed in 2004 and 2005, (Fig. 2) were treated according to the actual multimodal neoadjuvant schemes under the responsibility of the oncologists on the basis of the clinical presentation and thanks to a positive FNAB.

Recently also a third patient, 74 years old, coming to ambulance control for a swollen left arm (Fig. 3) and with the typical signs of IBC of the homologue breast, resulted positive to FNAB for IBC, and no surgical procedure was instituted. Instead she was committed to the oncologists for the neoadjuvant CT treatment.

None of the three last patients returned to our observation, but we hear that till now all are in regression of the clinical local symptoms.

Classical clinic presentation

Since the onset the disease displays mainly as an inflammation of the breast, with progressive and generally diffuse hardening of the interested mamma, which is of increased volume, reddish on the surface and warmer than the other skin surfaces. The skin may show a collateral vascularisation, and is discoloured from pale pink to brownish or to violet, also beyond the limits of the gland. The discoloration and oedema are more evident on the inferior aspect, sometimes resembling an erysipelas⁵. The skin patterns of cellulites can be present and sometimes also "peau d'orange" and nipple distortion. General conditions are not affected but fever and leukocytosis are possible, while the pain is either mild or totally absent. Palpation generally doesn't reveal the presence of a mass but only an increased consistence of part or all the gland. Lymph nodes are enlarged and palpable in 75% of cases, 95% in the axilla and 40% supraclavicular, although their absence or presence isn't determinant for diagnosis. Only 25% of the patients show distant metastases at the first presentation.



Fig. 1: Case n° 1 – IBC in a middle age nulliparous woman. It is evident the mamma enlargement and the pink coloration of the skin, without nipple deformation.

Fig. 2: Case n° 2 – Clinical presentation of IBC in the older of the two women. Meaningful are the skin coloration, the "peau d'orange" and the nipple retraction.

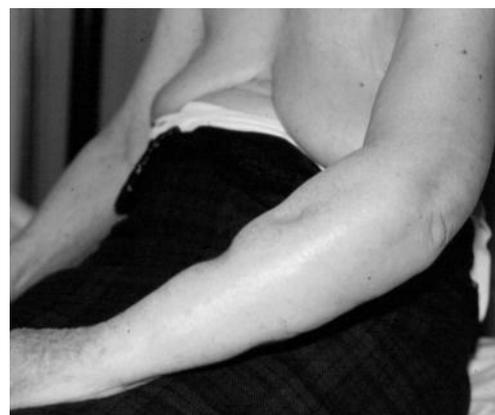


Fig. 3: Case n° 3 – Swollen left arm and IBC of the left breast.

Often the first approach to the patient of the practitioner is an antibiotic prescription thinking of a mammary abscess, before consulting a surgeon, and this delays the onset of the correct diagnostic procedure and the best treatment possible.

Differently from the evolution of the typical breast cancer, IBC develops and progresses very quickly, and as a rule the evolution is fatal in 6-12 months.

In fact IBC is not a true inflammatory disease, but is characterized by a precocious infiltration of dermal lymph vessel with neoplastic emboli for a particular dermatropism of the tumour cells, while the erythema mimicking an inflammatory disease may be a consequence of unknown toxins.

Pathology

No signs of suppuration are present in the gland, although there is a diffuse infiltrating oedema of all glandular parenchyma with minimal or absent stromal reaction, and absence of leukocytes and neutrophils near the tumour. Microscopically a precocious dermal and sub dermal lymph vessel invasion by neoplastic emboli is evident (Fig. 4). In 92% of cases the breast tumour is a ductal or lobular infiltrating highly undifferentiated carcinoma with fast cellular growth. The principal difference with other breast cancer is the particular and precocious lymphatic tropism of the rapid growing tumour cell, explaining the poor efficacy of the surgical treatment alone ⁶.

It is very difficult to obtain information on receptorial condition mainly for the scarce bioptic material available. Anyway IBC is almost always devoid of estrogens and progesterone receptors.

The TNM classification put the disease to T4d.

In 75% of the patients is possible to observe axillary lymph nodes metastases to witness the quick growth of the tumour. Also in 15% of the patients without lymph node metastases there are anyway Neoplastic micro-emboli in the tissues surrounding the primary tumour.

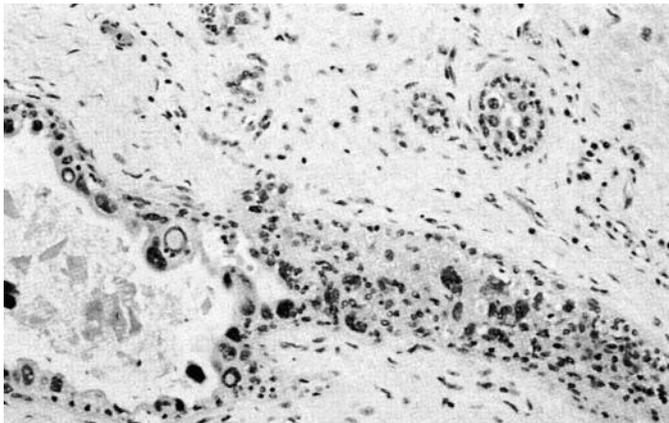


Fig. 4: Neoplastic emboli infiltrate many tiny lymph vessels among an oedematous glad stroma.

Diagnosis

Diagnosis is initially clinic ⁷. The disease can characterize for erythema and local oedema, and or neoplastic micro-emboli in dermal linfatics, either only embolization of deep lymph nodes. It is possible also the only lymph vessel neoplastic embolization without erythema and oedema. In these cases of "occult inflammatory breast cancer" the prognosis is somehow less severe.

In case of male disease the mammary tissue becomes thickened with skin erythema.

Definitive diagnosis is possible with FNAB or "trough cut" biopsy of the gland or of the nodes. The surgical biopsy of all layers of the gland, from the skin, gives more easily a sure pathologic diagnosis, demonstrating the embolization of the dermal lymph vessels and possibly of the gland itself, but exposes the wound to a very problematic healing, so retarding the start of the correct treatment. Therefore the surgical biopsy is permitted and advisable only if the diagnosis with less invasive methods escapes.

ECHOGRAPHY is generally useless for the diagnosis of IBC, moreover in menopause and in the absence of a particular mass to study. In other case it is possible to localize a ipoechogenic, irregular and scarcely definite mass, a skin thickening, an enhanced echo of the subcutaneous fat (Fig. 5), or to demonstrate the presence of tubular dilated vessels near the surface.

Echo-color-doppler can show a thriving vascularisation due to the inflammatory hyperaemia.

MAMMOGRAPHY is far more useful, as sometimes demonstrates a nodular mass in the breast with malignant micro calcifications. As a rule it shows oedema and a characteristic thickening of the above skin; can show also a diffuse enhancement of gland density with trabecular thickening and distortion or an asymmetric focal increased density.

Axillary lymph node enlargement can also be revealed. Cytological examination must be in general done without a precise palpable mass in the breast, and therefore not often useful. More advisable is the FNAB of an axillary pathologic lymph node, under echo-control, possible also on outpatients. If axillary nodes are only affected by a reactive inflammation, the examination can be repeated after few days.

Only if also lymph node cytology results negative, and the suspect of IBC remains, the surgical biopsy can be considered. It is often very useful in these cases but the consequent wound heals very slowly with lymph discharge and delays the possibility to begin the needed neo-adjuvant therapy. Therefore it is more convenient a surgical axillary nodes biopsy if they are enlarged.

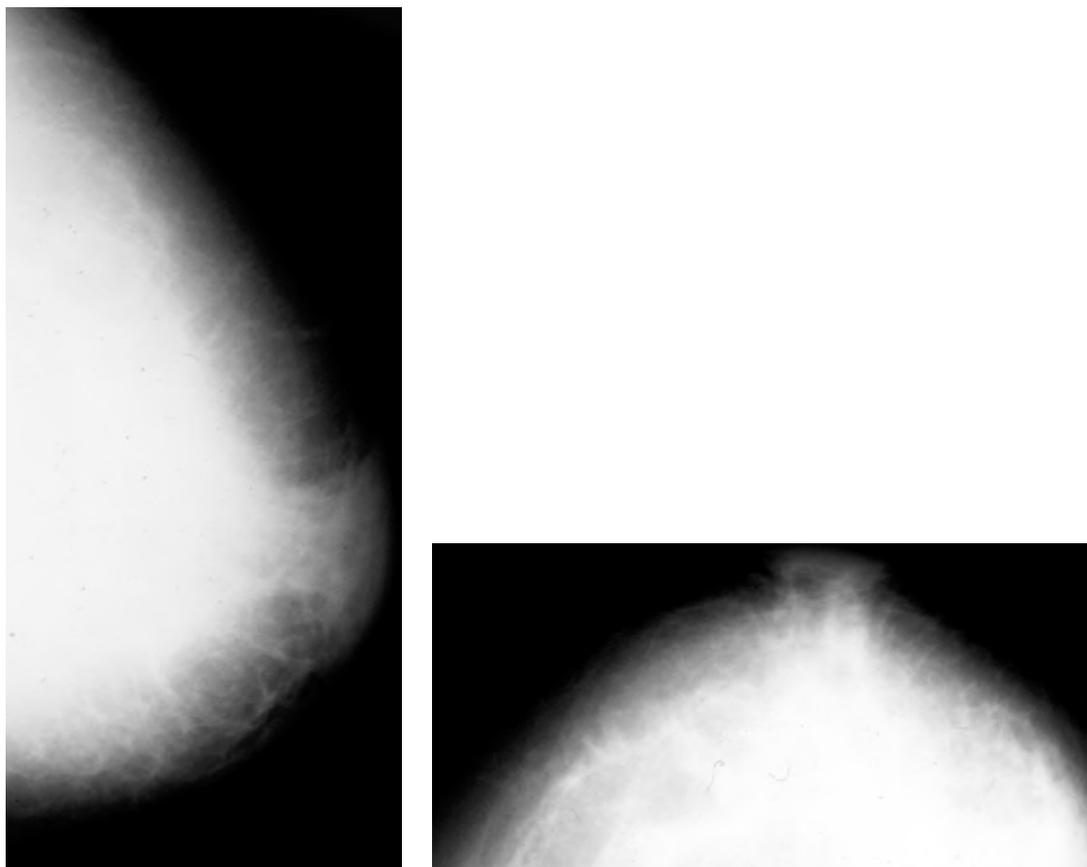


Fig. 5: Case n° 1 – Mammography demonstrates the density of the gland and the infiltration of the subcutaneous vessels responsible of the high grade oedema.

Prognosis

Some signs in IBC that suggest a worse prognosis. They are diffuse erythema on the skin of the whole mamma, volume of the tumour, presence of positive lymph node in the axilla, and permanence of erythema after the initial chemotherapy.

Natural prognosis is very bad. with mean mortality at 12-24 months as for N3, and no 5 years survival.

Lymph vessels thrombosis without the classical clinical presentation has a better prognosis.

Treatment of IBC

It is now well known since 1924 that surgical treatment is not useful as first or unique procedure, for the final outcome and also for the high incidence of local recidives. The disease itself was still described by Haagensen in 1960 as inoperable, as surgery never attains the healing nor free disease margins. The same surgical hormonal-therapy alone was substantially ineffective. Moreover the healing of the wound is problematic and the low immunological defences make easy a super infection. In the past radiotherapy alone demonstrated not too efficacious, but somehow useful to prepare for palliative surgery. Radical mastectomy might follow RT when there was an ameliorations of the tissue situation and absen-

ce of distant metastases from 4 to 8 weeks from the beginning.

Some morbidity follows RT and radical surgery, with delayed wound healing, local infections, scarring of the tissues with lymph stasis in the arm ⁸.

The results were not brilliant, with 22% 2 years survival, but not so long disease free. Moreover adjuvant chemotherapy, that could attain a certain further positive but temporary result only in 33% of cases, was often not possible at full doses.

Steps toward the actual scheme of therapy

Must be remembered that to start treating ex-juvantibus a patient with antibiotics and anti inflammatory drugs for two weeks before the definition of the right diagnosis is not only useless, but also negative because can be retarded the beginning of what is now considered the right therapeutic strategy.

As soon as the instrumental and histological diagnosis of IBC is sure, it is necessary to stadiate the patient for lymph node involvement and distant metastases, then an aggressive chemotherapy is started, followed, when possible, by radical RT or possibly by surgery. An optimal mean of stadiation can be now CT and 18-FG PET ⁹. The old scheme was Surgery + RT + CT, but the results were constantly very poor.

Actual scheme of therapy

It is substantially a multimodal and neoadjuvant strategy. Chemotherapy is preferred at the start to RT because of the presence still at the time of diagnosis of distant micro metastases.

Chemo- and Radio-therapy in succession gives a double or three fold survival, at acceptable quality of life. Radiotherapy by itself can reduce the tumour mass, making operable a tumour previously inoperable.

All actual researches point to state the best schedule and succession of cycles of induction chemotherapy, the selection and doses of drugs in polichemotherapy, the schemes of radiotherapy, the number of cycles, and the role itself of the possible final surgery.

Phase I – Aggressive CT

Phase II – Radical RT

Phase III – Surgery when possible and needed

Results

With radiotherapy and surgery alone the mean survival was 1,2 years, with 68% relapses in the following months (42% at six months).

With multimodal treatment 2 years survival attains 80% and 5 years disease free survival is 30%.

Conclusions

The first case of our observation confirms that also a radical enlarged Halstead's mastectomy is completely useless for any therapeutic advantage in IBC. The subsequent observations witness the high opportunity of institute a multidisciplinary treatment, and the marginal meaning of surgery.

It is very important to define a sure diagnosis of IBC, to start timely and opportunely a multimodal neoadjuvant treatment that only gives the hope of efficaciousness.

May be that IBC is a systemic disease from the beginning, well different from a locally advanced breast cancer, and that effectiveness of treatment is at the end illusory. Anyway a therapy must be done, at least for the psychological support of the patient, on condition that a minimal quality of life be preserved. Surgery has a collateral role in consideration of the difficult local control with the systemic therapy.

Every effort must be done for a local control of the disease, an attempt of a systemic positive effect, ever considering the quality of life of the patients.

The effectiveness of the treatments are to day better controlled step by step by the PET technology.

Riassunto

La definizione originale di mastite carcinomatosa sottolinea la principale causa di difficoltà diagnostica in questa situazione oncologica. In effetti sarebbe più corretto definirlo cancro infiammatorio del seno, per non evidenziarne troppo l'aspetto infiammatorio. Si tratta infatti di un vero cancro diffuso del seno, per il quale la terapia chirurgica rappresenta una risorsa del tutto marginale.

Oggi è infatti codificato che la mastectomia radicale è da considerare inefficace, in quanto soltanto una associazione di CT e del RT può offrire risultati di sopravvivenza accettabili.

Purtroppo però, non è corretto iniziare il trattamento antineoplastico multi disciplinare, se non dopo una conferma diagnostica cito-istologica; va poi evitato un tentativo farmacologico antiflogistico che può risultare ingannevole, e determinare una perdita di tempo prezioso per l'inizio della terapia corretta.

La chirurgia mirata al prelievo istologico rimane l'unico mezzo per una diagnosi corretta nei casi in cui con l'FNAB si dovessero avere esiti falsi negativi, ma sarebbe preferibile esaminare preventivamente i linfonodi per evitare che, dopo la biopsia, il drenaggio (in questi casi cospicuo) dal parenchima del seno possa determinare un ulteriore ritardo per avviare l'inizio del trattamento.

References

- 1) Pabst I: *Patologia mammaria*. Santiago de Chile, 1971.
- 2) Lee BJ, Tannenbaum NE: *Inflammatory carcinoma of the breast*. Surg Gynaecol Obstet, 1924; 39:580-95.
- 3) Mourali N, Muenz IR, Tabbane F, et al.: *Epidemiologic features of rapidly progressing breast cancer in Tunisia*. Cancer, 1980; 46:2741-746.
- 4) Juret P, Hayem H, Flaisler A: *A propos de 150 implantation d'yttrium radio-actif intra-hypophysaire dans le traitement du cancer du sein à une stade avancé*. J Chir, 1964; 84(4):409-33.
- 5) Rabindranath Nambi, Shiramuhi Tharakaram: *Carcinoma erysipeloïdes as a presenting feature of breast carcinoma*. Int J Dermatol, 1999; 38:367-76.
- 6) Mattheiem W: *Inflammatory breast cancer*. Ann Ital Chir, 1992; 63/2:115-17.
- 7) Ciatto S, Modena S, Molino A, Pacini P: *Diagnostica e terapia senologica*. Roma: CIC Edizioni Internazionali, 1997.
- 8) Ueno NT, Buzdar AU, Singletary SE, Ames FC, McNeese MD, Holmes FA, Theriault RL, Strom EA, Wasaff BJ, Asmar L, Frye D, Nortobagyi GN: *Combined modality treatment of inflammatory breast carcinoma: twenty years of experience at M.D. Anderson Cancer Center*. Houston, Texas Cancer Chemother Pharmacol, 1997; 40:321-29.
- 9) Balsami MM, Bakheet SM, Bakheet R, Ezzat A, El-Foudeh M, Tulbah A: *18-Fluorodeoxyglucose-Positron Emission Tomography in Inflammatory Breast*. World J Surg, 2003; 2710:1099-104.

