Clip placement in breast imaging: What we need to know.

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Learning objectives

1. Understanding the composition of radiographic biopsy markers, which are placed following breast biopsy.

2. Being aware of the histological appearance of breast markers in excised specimens and the variable types of inflammatory responses that can be associated with them.

3. Understand the potential for inflammatory histopathological change to obscure tumour characteristics.
Background

Radiographic biopsy markers used are available in many different forms, some of which contain metallic clips made of titanium or stainless steel. In addition pellets of resorbable polylactic acid (PLA) or polyglycolic acid (PGA) are used to help fix the marker in position, particularly if a cavity has been produced at the time of biopsy (1,2,3,4). Markers are often placed to localise small masses, areas of architectural distortion and micro calcifications, which once biopsied would be difficult to re-locate using imaging alone.

During histopathological assessment of excised breast specimens, these markers are rarely directly visualised at the macroscopic and the microscopic level, often falling out of the specimen during preparation. The markers are also commonly associated with inflammatory reactions, which fluctuate widely between specimens. In the absence of a visible tissue marker in excised specimens, pathologists rely on the specific sites of inflammation and a biopsy track to identify the site of initial biopsy and to assist with localisation of the tumour.

These differing inflammatory reactions have implications for both pathologists and radiologists especially regarding the reporting of suspicious breast lesions.

The presence of a marker has the potential to distort the original appearance of the lesion (5), especially when the reaction is florid histologically. It is also important to identify the marker site which typically corresponds to the initial biopsy site as it assists with radiopathological correlation and localisation of the tumour.
Findings and procedure details

In our study, we reviewed all breast excision cases which contained biopsy markers that came to our attention between January 2013 and October 2016. They included resection specimens which were examined by two pathologists. The type of material in the marker site was recorded and the associated degree on inflammation on a scale of 1 to 3 (1=mild; 2=moderate; 3=florid - Fig. 1). 4 different types of inflammatory responses were also recorded (Fig 2)

Fig. 2: The four types of inflammatory reaction observed; A: Lakes of eosinophilic acellular material surrounded by collagen deposition, marked fibrosis and some lymphoplasmacytic inflammation (Type 1, H&E, 40x); B: Washed out colourless material with a prominent foreign body type giant cell reaction and lymphoplasmacytic inflammation (Type 2, H&E, 40x); C: Polarisable suture like material surrounded by lymphoplasmacytic inflammation and a small component of foreign body type giant cells (Type 3, H&E, 100x); D: Large fragments of polarisable material with a predominantly foreign body giant cell reaction (Type 4, H&E, 40x).

References: Pathology Department, Royal North Shore Hospital, Sydney, Australia.

Type 1: **Acellular material** surrounded by fibrosis and collagen deposition

Type 2: **Colourless material** surrounded by florid foreign body type giant cell reaction and lymphoplasmacytic inflammation

Type 3: **Polarisable suture like material** surrounded by lymphoplasmacytic inflammation and a mild foreign body type giant cell reaction

Type 4: **Large fragments of polarisable material** with a predominantly foreign body giant cell reaction.

The biopsy markers consisted of 3 types:

a) **Bard Gel Mark Ultra marker**: contains 5 to 10 resorbable PLA or PGA pellets including one with an embedded radiopaque marker composed of either stainless steel or titanium(3) Fig 3
Fig. 3: Photograph of Gel Mark Ultra clip and PGA/PLA bio absorbable pellets

References: BARD AUSTRALIA

b) **Bard SenoMark Ultra marker**: deploys 3 resorbable PGA pads with the center pad containing a Titanium or BioDur TM 108 wireform with an interwoven polyvinyl alcohol (PVA) polymer (3) Fig 4

Fig. 4: Photograph of SenoMark Ultraclip attached to central bio absorbable PGA pad.

References: BARD AUSTRALIA

c) **Hologic SecurMark marker**: composed of an outer bio-absorbable suture-like netting material and internal permanent marker made of titanium or stainless steel (4) Fig 5

Fig. 5: Photograph of several different styles of marker with expanded bio absorbable netting around one style of clip.

References: Hologic Australia

**RESULTS**

A total of 22 patients were included, 2 of which has two separate tissue markers inserted. In all the patients, the tissue markers were inserted during core biopsy of visible lesions or microcalcifications. The core biopsy results of these patients included radial scar, ductal carcinoma in situ and invasive carcinoma.

14 cases had the Bard Gel Mark Ultra marker used and 7 had the Bard SenoMark marker including two patients who had one of each type. The Hologic SecurMark markers were used in 3 patients undergoing stereotactic guided biopsy of microcalcifications.

There was a weak but statistically significant association between the length of time that the marker was in-situ and the type of reaction. Type 1 reactions with fibrosis and collagen deposition were more likely to be associated with longer marker insertion whereas types 3 and 4 with foreign body type giant cells were associated with shorter clip insertion time ($p=0.026$). There were no other significant associations either between clip type used and type of reaction ($p=0.432$) or between the clip type and the degree of inflammation ($p=0.422$). Similarly, there was no significant association between the time the clip spent in-situ and the **degree** of inflammation ($p=0.627$). In 2 patients, the inflammatory response to the tissue marker was so florid that it obscured the tumour.
DISCUSSION

The series shows that the inflammatory responses surrounding tissue markers in excised breast specimens are often secondary to the stabilising materials (such as: PLA pellets, PGA pellets; external suture like netting material surrounding the metallic markers). The type and grade of inflammatory reaction however can range from mild to florid and is independent of the composition of the markers. As markers often fall out during histopathology preparation of excised breast specimens, the inflammation surrounding the site of the marker and hence the initial biopsy help pathologists locate the tumour in the excised specimens. It also documents the site of initial biopsy performed by radiologists.

In our series of patients, there was marked variability in the type and extent of inflammatory reactions surrounding the tissue markers in the excised specimens. Despite having the same type of marker inserted at the time of biopsy, the type of foreign body reaction that was recorded in the marker site and the degree of inflammation varied significant between patients. Two patients in our series experienced such florid inflammatory response to the marker in the excised specimens that it obscured the initial tumour which was seen on the core biopsy.

We did observe a weak relationship between the length of time the marker was in situ and the type of inflammatory reaction which was observed. Patients who had biopsy markers in situ for longer periods of time had inflammatory reactions which consisted of marked fibrosis and lymphoplasmacytic inflammation (reaction type 1). Patients who had the marker placed for a shorter period of time more commonly had giant cell type reactions (reaction type 3 and 4).

However, we did not find a significant relationship between the grade of inflammation and the number of days the markers were in situ.

We believe that the inflammatory response is largely patient dependant rather than time dependant. We observed the same type and grade of inflammatory reaction in 2 patients who had 2 separate tissue markers placed to localise separate lesions.

One patient had the first marker (Bard SenoMark-omega shape) inserted following stereotactic biopsy of microcalcifications but the core biopsy samples did not demonstrate representative microcalcifications in the specimen x-ray. A repeat stereotactic biopsy was then performed on the same date and a second Bard SenoMark tissue (oval shaped) marker was deployed approximately 6cm from the original tissue marker. Histopathological analysis of the initial wide local excision specimen as well as the
mastectomy specimen both showed florid inflammatory responses of reaction type 3. The time frame between the two histopathology analyses of both specimens was 56 days.

Similarly, the second patient had two separate clips inserted into both breasts to localise different lesions on the same date. Both lesions were excised 42 days apart but histopathology analysis demonstrated mild inflammatory reaction surrounding the tissue markers in both excised specimens.

These two cases highlight the likelihood that the amount of inflammatory recruitment may be a personalised host response by the body’s immune system to the tissue marker. The grade of inflammation associated with tissue markers is therefore not time dependant but different for each patient.
Fig. 1: The three grades of inflammation; A: Mild inflammatory response (H&E, 40x); B: Moderate inflammatory response (H&E, 40x); C: Florid inflammatory response (H&E, 40x).

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Fig. 2: The four types of inflammatory reaction observed; A: Lakes of eosinophilic acellular material surrounded by collagen deposition, marked fibrosis and some lymphoplasmacytic inflammation (Type 1, H&E, 40x); B: Washed out colourless material with a prominent foreign body type giant cell reaction and lymphoplasmacytic inflammation (Type 2, H&E, 40x); C: Polarisable suture like material surrounded by lymphoplasmacytic inflammation and a small component of foreign body type giant cells (Type 3, H&E, 100x); D: Large fragments of polarisable material with a predominantly foreign body giant cell reaction (Type 4, H&E, 40x).

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**Fig. 3:** Photograph of Gel Mark Ultra clip and PGA/PLA bio absorbable pellets

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**Fig. 4:** Photograph of SenoMark Ultraclip attached to central bio absorbable PGA pad.

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**Fig. 5:** Photograph of several different styles of marker with expanded bio absorbable netting around one style of clip.

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Conclusion

We would like to create awareness of the varying types of inflammatory responses to tissue markers observed during histopathology assessment of excised breast specimens. The presence of the histological reactions can be useful to direct pathologists to the region of biopsy in the surgically excised specimen.

Our series shows that the different types and composition of markers used and the length of time it remains in situ has no significant relationship to the degree and only minor effect on the type of inflammatory response. The degree of inflammation appears to be related to patient factors including the host immune response to the tissue marker.
References


