Clinical management of radial scar without atypia diagnosed on core needle biopsy

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Abstract: Radial scars (RS) are benign breast lesions that may be associated with other proliferative changes and sometimes carcinoma. They are frequently evaluated with core needle biopsy (CNB) due to their similar appearance to carcinoma on mammography. The upgrade rates to malignancy and high risk lesions (HRL) upon excision of RS are highly variable, influenced by various patient, biopsy, and pathologic factors. The presence of atypia significantly increases the malignant upgrade risk, and all RS with atypia should be considered for excision. The management of RS without atypia diagnosed on CNB is more controversial. Based on a review of the recent literature, the malignant upgrade rate of pure RS is low at 5% or less and is further reduced by using vacuum-assisted biopsy (VAB). The upgrade rate to HRL is higher at 12–26%, and may have treatment implications with regards to enhanced breast cancer screening and risk reducing strategies. In this paper, we have proposed a management algorithm of pure RS diagnosed on CNB. The factors to consider include imaging-pathologic concordance, size of the RS, biopsy method, and whether the patient is healthy or willing to consider risk-reducing strategies. The decision to excise, observe, or re-biopsy with VAB should be made on an individual basis.

Keywords: Radial scar (RS); malignant upgrade; high risk lesions (HRL); excisional biopsy

Introduction

Radial scars (RS), also known as complex sclerosing lesions, are benign proliferative breast lesions and are usually asymptomatic in healthy women. In the pre-mammographic screening era, they usually presented as incidental findings in breast specimens that were surgically excised for unrelated conditions. Since the introduction of screening mammography, RS has increasingly become a screen-detected lesion, and its detection has increased even more with the adoption of digital breast tomosynthesis (DBT). Because of its spiculated appearance on mammography, which can mimic breast cancer, RS is often evaluated with core needle biopsy (CNB).

Because of the significant upgrade risk to malignancy, it is generally accepted that RS with atypia should be excised. The management of RS without atypia is more controversial. The risk of association with malignancy in pure RS ranges widely in the literature and may be related to various patient, imaging, biopsy, and pathologic factors. This paper serves as a review of the clinical evidence regarding the management of CNB-diagnosed pure RS. In addition, we have proposed a management algorithm of these lesions.

Incidence

In autopsy studies, the frequency of RS ranges from 14% to

43%, depending on the amount of tissue examined, and RS is frequently multicentric or bilateral (1,2). The reported incidence of RS from screening mammograms is 0.3–0.9 per 1,000 women screened (3). In a series of 10,921 image-guided needle biopsies, pure RS accounted for 0.8% (4), and in another series of 4,458 consecutive image-guided needle biopsies, it accounted for 1.8% (5).

Imaging

The mammographic diagnosis of RS has been defined by a set of criteria put forth by Tabar and Dean (6): (I) varying appearance in different projections; (II) absence of solid dense central mass; (III) presence of long thin spicules; (IV) radiolucent linear structures parallel to radiopaque spicules (i.e., "black star" appearance); (V) absence of palpable lesions or skin changes. None of these findings is specific for RS, as many studies have shown inaccurate radiologic classification based on some of these criteria (7-9). Since the appearance of RS mimics that of invasive breast cancer despite various imaging criteria, CNB is often required to distinguish the two entities.

Microcalcifications may occur in RS, even though their absence had been suggested in the past to be a feature of RS (10). They are usually associated with benign proliferative changes and are nonspecific with respect to differentiating RS from malignancy. In some cases, the microcalcifications may be the only abnormality on imaging, and RS becomes an incidental pathologic finding upon stereotactic CNB (10-12).

DBT has been shown to detect malignant neoplasms at a higher rate than digital two-dimensional mammography (DM), due to its ability to better characterize masses and architectural distortions (*Figure 1*). Not surprisingly, the rate of identifying RS on DBT has increased compared to DM (13,14). In Phantana-Angkool *et al.*'s study of 301,133 consecutive mammograms between 2007 to 2017 (179,085 DM, 122,048 DBT), the detection rate of pure RS significantly increased from 0.04% to 0.13% with DBT (P<0.0001). However, the upgrade rate to malignancy was not statistically different between DM and DBT (6% *vs.* 3%, P=0.24); nor was the upgrade rate to a high risk lesion (HRL) (12% *vs.* 22%, P=0.10) (13). The similar rate of upstaging despite an increase in detection with DBT suggests that there are no reliable DBT-specific features to distinguish RS from malignancy even on modern mammography.

RS may be visible on ultrasound in only half of the cases, and, when visible, often presents as an irregular hypoechoic mass with indistinct margins with or without shadowing (15,16). There are no sonographic features that can reliably differentiate RS from malignancy, but an ultrasound should always be performed when there is an area of architectural distortion on mammography. If a mass is identified on ultrasound, it can serve as the target for ultrasound-guided CNB.

The presentation of RS on breast MRI includes masses (50%), architectural distortions, non-mass lesions, and single foci, with variable enhancement patterns (17). Just as in mammography and ultrasonography, most MRI characteristics of RS are suspicious. It has been suggested that the absence of MRI enhancement of a lesion suspected to be RS may predict a benign excision result (18-20). In a study of 169 HRLs including 42 RS, the negative predictive value of MRI for RS was 97.6%, and the one false-negative case was upgraded to low grade ductal carcinoma in situ (DCIS) (18). A similarly high negative predictive value of 97% was reported by Londero *et al.*, and only one of the 31 non-enhancing RS was upgraded to low grade DCIS as well (20). Thus, nonsurgical management may be considered for CNB-diagnosed pure RS, when MRI is negative for any abnormal findings. However, the high cost of breast MRI and lack of wide availability limit its usefulness.
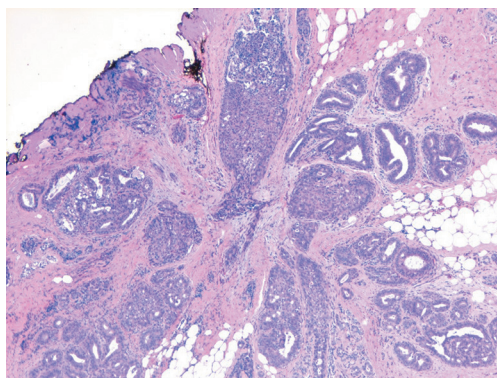
Pathology

Histologically, RS is characterized by a fibroelastic core with surrounding radiating spokes of ducts and lobules, which often contain a variety of proliferative changes, such as epithelial hyperplasia, duct ectasia, adenosis, and cysts (3) (*Figure 2*). These lesions may be associated with epithelial atypia or in situ or invasive carcinoma, and the entrapped central glandular elements, especially when proliferative changes are present, may give the appearance of tubular carcinoma. The benignity of the lesion can be demonstrated by an intact myoepithelial cell layer on immunohistochemistry staining. It is generally accepted that a RS larger than one centimeter on pathology is called a complex sclerosing lesion, whereas lesions 1 cm or smaller are called RS. Although most RS are microscopic findings, some can achieve a size that makes them visible on imaging.

Biologic relevance

Over the years, the biologic relevance of RS and their relationship to breast cancer have been much debated. On the basis of existing literature, there are several "truths" to the nature of RS. First, RS is not a premalignant lesion.
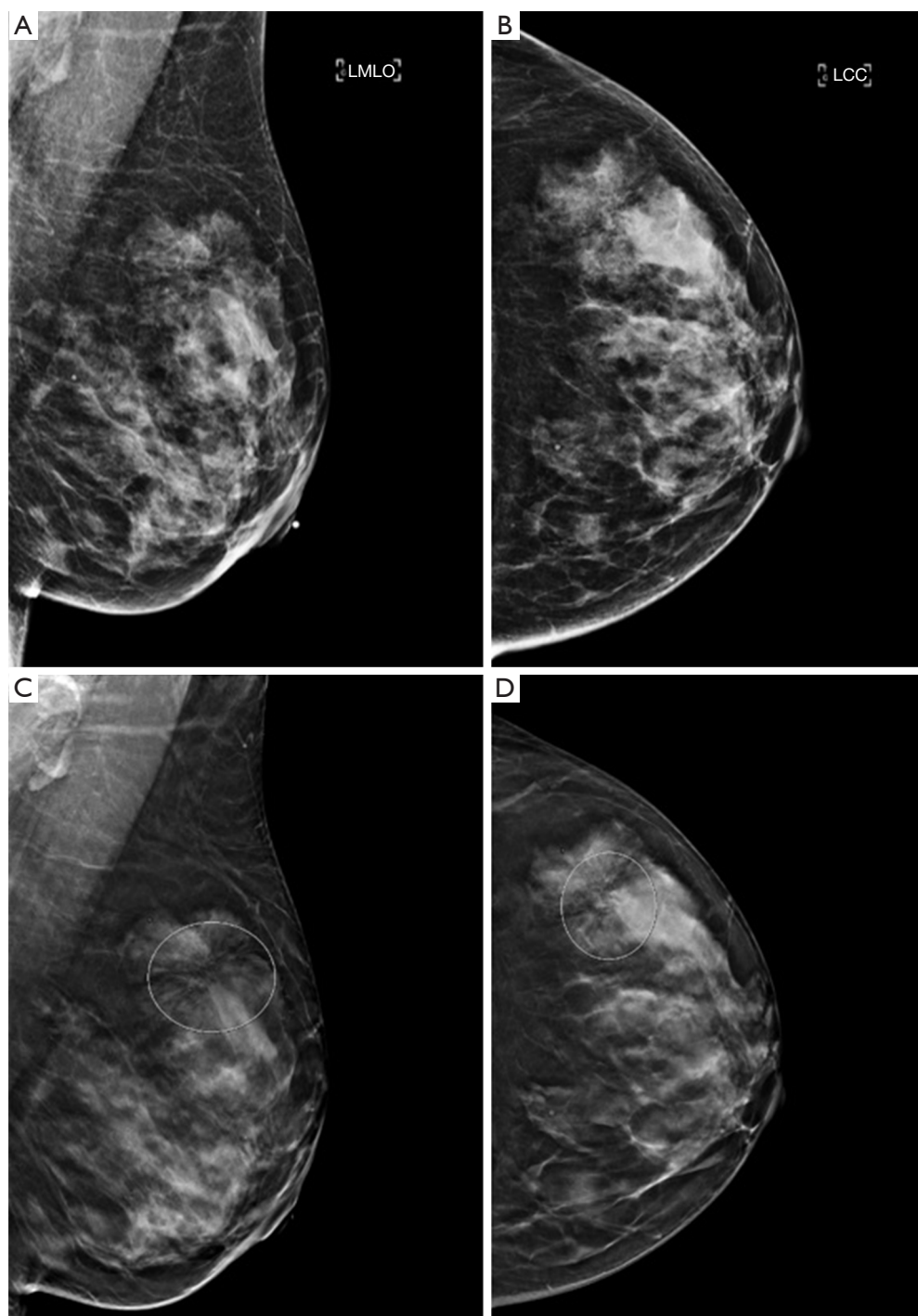
Figure 1 Appearance of radial scar on digital two-dimensional mammography (A, mediolateral oblique; B, craniocaudal) and digital breast tomosynthesis (C, mediolateral oblique; D, craniocaudal). The architectural distortion is better seen on digital breast tomosynthesis, which demonstrates the classic features of radial scar including the presence of central lucency with thin long spicules radiating outward.

Figure 2 Histologic appearance of radial scar which is characterized by a fibroelastic core with surrounding radiating spokes of ducts and lobules, which often contain a variety of proliferative changes. Hematoxylin & eosin stain, 4× magnification.

The morphologic similarity to carcinoma, especially tubular carcinoma, and the presence of carcinoma in some RS had led to the hypothesis that RS could represent a direct precursor to carcinoma (21,22). That theory has been debunked by several later studies, none of which found transitional features of RS to carcinoma (1,2,23,24).

Second, RS frequently coexists with other proliferative lesions and sometimes carcinoma. The frequency of association with malignancy has been reported to be as high as 45% (25), although the upgrade risk reported in a recent meta-analysis is much lower at 5% or less for pure RS (26). The high malignancy rates have led many to conclude that all RS should be excised, a practice pattern that has been questioned in recent years.

Third, RS does not impart an increased breast cancer risk above that of the associated proliferative changes. A case-control study of 99 women with RS within the Nurses' Health Study had suggested that RS was an independent risk factor for breast cancer (27). In this study by Jacobs et al., the relative risk (RR) for women with proliferative disease and RS was 3.0, and, for women with proliferative disease alone, was 1.5. The risk was similarly increased for atypia and RS, compared to atypia alone (RR 5.8 vs. 3.8). A much larger study by Sanders et al. as part of the Nashville Breast Cohort showed contrary results (28). In this study of 880 women with RS, the overall risk of breast cancer associated with RS was 1.82, and RS was not found to have an additive risk and was not an independent risk factor for carcinoma. Specifically, the RR associated with proliferative disease alone was 1.74 and was 2.13 when RS was present; RR for atypia with RS was 5.39, not significantly different from RR of 4.38 for atypia

alone. Similar findings were seen in a Mayo Clinic study of 439 women with RS, which showed no increased breast cancer risk associated with RS aside from that imparted by the accompanying proliferative changes (29).

Management

The upgrade rate to malignancy at surgical excision of RS diagnosed from CNB varies from 0 to 45% (26) and has led to widely varying practice patterns. Such wide variation in upgrade rates is confounded by the presence of atypia, sampling method, biopsy device and gauge, number of samples, criteria for subsequent excision, and imaging-pathologic concordance. The presence of atypia with RS on CNB significantly increases the malignant upgrade rate (26,30). In a recent meta-analysis of 3,163 RS excised after CNB, the malignant upgrade rate for RS with atypia was 29% but only 5% for pure RS (26). Hence, RS with atypia diagnosed on CNB should be considered for excision. In the United States, surgical excision of RS with high risk features is standard practice. However, management of pure RS remains controversial. In 2016, the American Society of Breast Surgeons released a consensus guideline recommending excision of most RS, although small, well-sampled lesions with large-gauge devices may be followed with imaging (31). However, the lack of consensus on what constitutes a "small" or "well-sampled" lesion in this statement highlights the difficulty in identifying a subset of RS at low enough risk of upgrade as to avoid surgical biopsy.

Table 1 summarizes the upgrade rates to malignancy and HRL including atypical ductal hyperplasia and lobular neoplasia in studies of at least 40 pure CNB-diagnosed RS done in the last 10 years. Whereas some earlier series had shown much higher malignant upgrade rates of up to 25% even for pure RS (47), the rates of malignant upgrade in this table range from 0% to 10.5%, with more recent studies showing lower upgrade rates than earlier ones. In the series from 2016 on, the malignant upgrade rates for pure RS were all 5% or less.

Stringent exclusion of atypia on CNB and increased extent of sampling likely account for the low upgrade rates in the recent times. Several single-institution series showed larger gauge biopsy devices and more core samples reduced the upgrade rate (47-49). Farshid et al.'s meta-analysis stratified 3,163 RS into three subgroups by CNB gauge, 14 G, a mix of 8–16 G, and vacuum-assisted biopsy (VAB) 8–11 G, and showed a stepwise decrease in malignant upgrade rates for pure RS, 5%, 2%, and 1% respectively (26). It is intuitive that using a larger gauge needle or obtaining more cores would produce more comprehensive sampling of the lesion

Table 1 Upgrade rates to malignancy and high risk lesions (HRL) of pure radial scar (RS) diagnosed on core needle biopsy (CNB)

| Study	Year	Number of RS excised/CNB	Device and gauge	Number of cores	Upgrade to invasive cancer	Upgrade to preinvasive cancer	Malignant upgrade rate (%)	HRL upgrade (%)
Linda (5)	2010	62/62	SL 14, VAB 11	SL 3–8, VAB 9–18	2/5	3/5	8	15
Osborn (32)	2011	95/95	SL 14, VAB unspecified gauge	1–10	4/7	3//7	7.3	16.8
Bianchi (33)	2012	49/49	SL 14	3–8	1/4	3/4	8.2	18.3
Morgan (34)	2012	67/67	SL11, VA 9	NS	2/6	4/6	9	NS
Andacoglu (35)	2013	67/67	Varied devices, 9–18	NS	0/4	4/4	5.9	22.4
Miller (36)	2014	102/131	SL 14, VAB 7–11	SL at least 5, VAB at least 4–6	1/2	1/2	2	21.6
Conlon (37)	2015	48/53	Varied devices, 9–14	NS	0/1	1/1	2	25
Matrai (38)	2015	77/77 (all ≤5 mm)	SL 14–22, VAB 7–11	NS	0	0	0	12
Nassar (39)	2015	38/100	SL11–14, VAB 9	4–12	2/4	2/4	10.5	18.4
Donaldson (40)	2016	37/57	SL 14, VAB 9–12	6–12	0	0	0	16
Hou (41)	2016	40/81	SL 14, VAB 8	3–5	0	0	0	22.5
Kim (4)	2016	63/88	VAB 8–14, most 9–11	4–6	0/1	1/1	1.6	NS
Leong (42)	2016	161/219	SL 14–16, VAB 9	SL at least 3, VAB 12	0/1	1/1	0.6	NS
Li (43)	2016	220/403	SL 14, VAB 9	SL 3–5, VAB 6–9	1/2	1/2	0.9	25.9
Chou (44)	2018	55/91	SL 14, VAB 9	NS	2/2	0/2	4	NS
Ha (45)	2018	37/53	SL 14, VAB 11	At least 5	0/2	2/2	5.4	5.4
Lamb (14)	2018	111/111	SL 14, VAB 9	NS	1/4	3/4	3.6	NS
Bacci (46)	2019	48/48	VAB 8–11	NS	0	0	0	25
Phantana-Angkool (13)	2019	223/223	SL14–18, VAB 9,	NS	6/8	2/8	3.6	18.8

SL, spring-loaded; VAB, vacuum-assisted biopsy; NS, not specified.

and hence reduce the upgrade rate upon excision.

Many recent studies, especially those utilizing VAB, have advocated non-surgical management of pure RS. When RS is diagnosed via a spring-loaded device, a repeat biopsy with VAB can be performed, and surgery can be avoided if the repeat biopsy is benign (50,51). In the United Kingdom, it is standard practice that RS with or without atypia diagnosed on CNB undergo vacuum-assisted excision (VAE) for small lesions or thorough sampling with VAB for larger lesions (52). If VAE is benign without atypia, the lesion is observed; if VAE shows atypia,

either observation or diagnostic surgery is considered, depending on the extent and degree of atypia. VAB can be a particularly useful tool for large RS, when surgical excision would result in significant deformity.

Other factors that have been associated with upgrade include age older than 53–64 years (34,38,43,45), lesion size larger than 1–2 cm (39,45,53), mammographic appearance with mass or architectural distortion versus calcifications (36), and non-incidental nature of RS (38,46). However, these findings are not consistent in the literature. By far, the strongest and the most consistent risk factor for
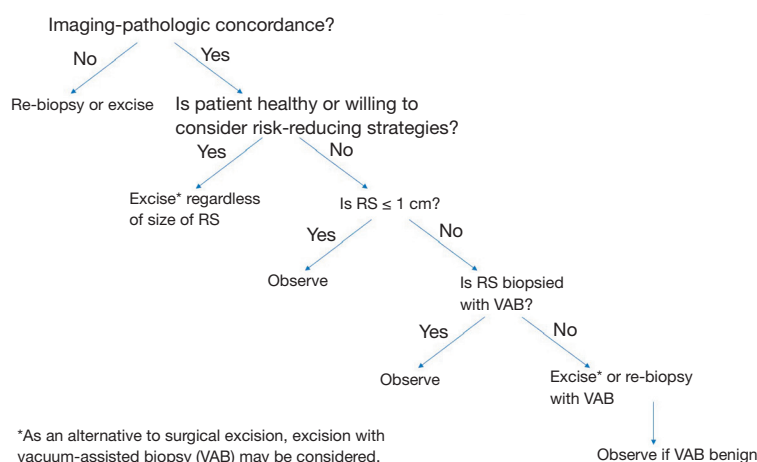
Figure 3 Management algorithm of radial scar without atypia diagnosed on core needle biopsy.

upgrade is the presence of atypia (26,30).

There is no consensus on an acceptable level of upgrade risk for avoidance of surgery. The BIRADs 3 category as used by the American College of Radiology designates a probably benign mammographic finding that has a 2% or less risk of malignancy (54), and short-term imaging surveillance is usually accepted for this category of lesions. In a meta-analysis of 11,423 high-risk (B3) lesions, the malignant upgrade rate of the 334 pure RS was 6% (30). The authors proposed that a 10% malignant risk was low enough to leave the lesion in the breast, and hence, pure RS could be observed. By these standards, most pure RS diagnosed on CNB in the modern era have a low enough risk of malignant upgrade that observation may be considered.

When breast cancers are detected on surgical excision for RS, they are usually small in size, low grade, hormone receptor-positive, and more likely to be preinvasive than invasive (5,13,36,43,44). If left in situ, these tumors with extremely favorable prognostic features may become apparent on close imaging surveillance, and later detection is unlikely to affect the overall outcome. Additionally, multiple studies showed that unexcised RS that were closely followed did not result in any malignancy, even at 11 years of follow-up (41,45,55), although RS recommended for observation may exhibit different features from RS recommended for surgical excision. The overall low rate of upgrade to malignancy and the extremely favorable features of these tumors suggest that many surgical excisions of RS can be avoided, if the goal of the procedure is only to rule out underlying malignancy.

However, finding associated HRL on surgical excision

may have treatment implications. The rates of upgrade to HRL on excision of RS are higher than the malignant upgrade rates, ranging from 12% to 26% in *Table 1*. In a study of 18 microscopic RS seen only on pathology from CNB and included in their entirety in the biopsy specimens, the malignant upgrade rate was 0, but the HRL rate was 39% (56). Even RS well sampled with VAB have an associated HRL rate of 25% (46). A diagnosis of atypical ductal hyperplasia, atypical lobular hyperplasia, or lobular carcinoma in situ is associated with an increased risk of breast cancer development in either breast. For women at increased risk of breast cancer, risk-reducing strategies may be considered, including chemoprevention agents and potentially risk-reducing surgery (57). Annual breast MRI screening may be considered in addition to annual mammography for women whose lifetime risk of breast cancer is 20% or greater (58). Hence, for women whose management decisions may change as a result of any HRL co-existing with RS, further diagnostic workup of RS with either surgical excision or VAB excision should be considered to rule out any underlying atypia.

There is no arbitrary threshold for surgical excision of pure RS. Each case should be evaluated on an individual basis and ideally be discussed at multidisciplinary tumor board. Assessing imaging-pathology concordance is essential, as is ruling out atypia on CNB. The goal and the rationale for excision should be discussed with every patient with RS, and the decision to excise, observe, or to repeat a biopsy with VAB be made accordingly.

In summary, we propose the following management of pure RS (*Figure 3*). For (relatively) healthy patients who

would benefit from chemoprevention and/or additional imaging screening if concomitant HRL is found, RS of all sizes should be excised; alternatively, VAB excision can be performed. For patients with significant comorbidities or those who would not consider risk reduction strategies, RS 1 cm or smaller or RS of any size sampled with VAB can be considered for observation. Larger RS should undergo surgical excision; as an alternative, repeat thorough sampling or excision with VAB can be considered, and the lesion can be observed if the repeat biopsy does not show carcinoma. If there is radiologic-pathologic discordance, either repeat biopsy or surgical excision should be performed. When carcinoma (invasive or preinvasive) is found on VAB excision, additional oncologic surgery must be performed. RS considered for observation or incompletely excised should undergo imaging follow-up, the interval of which should be discussed with the radiologist.

Conclusions

Pure RS diagnosed on CNB has a low risk of malignant upgrade (5% or less) on surgical excision, but the rate of upgrade to HRL is much higher (12–26%). The upgrade risk significantly increases with the presence of atypia, but can be reduced by sampling the lesion with a larger gauge biopsy needle, more cores, and VAB. RS of all sizes should be considered for surgical or VAB excision, if clinical management would change as a result of associated HRL. Otherwise, small (1 cm or less) or well sampled RS can be observed. Larger RS should be excised but can be considered for observation if repeat biopsy with VAB shows benign findings.

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Footnote

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