Editorial

Nanja Gotland
Department of breast surgery, Herlev-Gentofte Hospital, Gentofte, Denmark
Department of plastic- and breast surgery, Sealand University hospital Roskilde, Roskilde, Denmark
Anand Loya
Department of pathology, Rigshospitalet, København Ø, Denmark
Charlotte Lanng
Department of breast surgery, Herlev-Gentofte Hospital, Gentofte, Denmark
Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, København Ø, Denmark
Hanne Rønning
Department of breast surgery, Herlev-Gentofte Hospital, Gentofte, Denmark
Tove F. Tvedskov
Department of breast surgery, Herlev-Gentofte Hospital, Gentofte, Denmark
Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, København Ø, Denmark

Clinical Breast Cancer
Vol. 000, No.xxx, 1–3

Radiation Induced Atypical Vascular Lesion in the Breast

Introduction

Atypical vascular lesion (AVL) was in November 2019 classified by WHO as an independent diagnosis with specific diagnostic criteria (Table 1).[1] AVL develops in previously irradiated skin.[2–7] The incidence is low but increasing due to the increasing use of breast conserving surgery with radiotherapy in the treatment of breast cancer.[3,6,11]

There are no standard guidelines for surgical treatment of AVL, but due to a possible risk of developing angiosarcoma (AS) the literature recommends complete excision and close follow-up.[8-9] The evidence for development of AS is scarce and the incidence is unknown.

In this study we describe the incidence and treatment of AVL over a 10-year period to investigate whether the changes in WHO classification have led to a change in incidence of AVL diagnoses.

Submitted: Apr 8, 2022; Revised: Jul 18, 2022; Accepted: Aug 21, 2022; Epub: xxx

Address for correspondence: Tove F Tvedskov Dr. med, Phd, Department of breast surgery, Rigshospitalet/Herlev-Gentofte hospital, Inge Lehmanns vej 5, 2100 København Ø, Denmark.
E-mail contact: tove.holst.filtenborg.tvedskov@regionh.dk

Method

All patients diagnosed with AVL in the skin over the breast or surrounding irradiated skin at our institution between June 1, 2010 and June 31, 2020, was retrospectively identified in the Danish National Pathology Databank.[10] Our institution is one out of 2 hospitals in Denmark with specialist function in vascular tumors. Information on patient age at diagnosis, location, characteristics and treatment of AVL, breast cancer treatment, time since radiotherapy, length and method of follow up, and development of AS were

Table 1 AVL Criteria According to WHO Classification of Breast Tumors, fifth edition, 2019

Previously irradiated skin
Dermal-based vascular proliferation, rarely deep dermal
Relatively circumscribed
Irregular shaped thin-walled vascular spaces lined by a single layer of endothelial cells
Lack of infiltrative growth, cytological atypia and mitosis
No MYC overexpression by immunohistochemistry
No MYC amplification by FISH

1526-8209/$ - see front matter
https://doi.org/10.1016/j.clbc.2022.08.010

Please cite this article as: Nanja Gotland et al, Radiation Induced Atypical Vascular Lesion in the Breast, Clinical Breast Cancer, https://doi.org/10.1016/j.clbc.2022.08.010

Table 2 Patient, Treatment, and Lesion Characteristics of Patients Diagnosed With AVL According to Change in WHO Diagnosis

	Prior to WHO Changes n = 3	After WHO Changes n = 8	All Patients n = 11
Age, y			
Mean, (range)	52.33 (46-65)	73.29 (50-85)	67.45 (46-85)
Surgery (Breast cancer)			
BCS (%)	2 (66.7)	7 (87.5)	9 (81.8)
Mastectomy (%)	1 (33.3)	1 (12.5)	2 (18.2)
RTX Dose, Gy			
Mean (range)	60 (xxx)[a]	52.57 (40-66)	53.11 (40-66)
Latency interval, months			
Mean (range)	55 (43-77)	77 (1-188)	71 (1-188)
Site of vascular cutaneous lesion			
Breast (%)	2 (66.67)	7 (87.5)	9 (81.8)
Thorax wall (%)	1 (33.33)	1 (12.5)	2 (18.2)
Clinical presentation			
Plaque (%)	0 (0)	7 (87.5)	7 (63.6)
Nodulus %)	3 (100)	1 (12.5)	4 (36.4)
Size of AVL, cm			
Mean, (range)	0.6 (0.5-0.7)	10.96 (0.7-20)	8.14 (0.5-20)
Treatment			
Mastectomy (%)	0 (0)	3 (37.5)	3 (27.3)
Yearly PET/CT (%)	1 (33.3)	3 (37.5)	4 (36.3)
No further treatment (%)	1 (33.3)	2 (25)	3 (27.3)
Excision (%)	1 (33,3)	0 (0)	1 (9.1)
Follow-up, mo			
Mean (range)	46.97 (18.1-103.5)	11.95 (6-12.39)	22.05 (6-103.5)

[a] Information only available for one out of 3 cases.

collected from electronic patient files. Patients diagnosed with AS prior to, or at the time of AVL were excluded. Length of follow-up was calculated from date of diagnosis and censored on the date of loss to follow-up, death or June 7, 2021, whichever came first.

The incidence rate was estimated as the number of AVL incidences pr months at risk before and after the changes in WHO classification. Differences in patient characteristics were tested using student t-test by online calculator at https://www.socscistatistics.com/test

The study was approved by the Danish Data Protection Agency (record no. 2014-41-3376) and the Danish health authorities (Journal-nr.: R-20055567). All patients have been contacted and permission for use of data have been given.

Results

In total, 13 cases with AVL were identified in the 10-year period. Two cases were diagnosed with AS at the time for AVL and were excluded. Thus, 11 cases were included in the study. Characteristics are summarized in Table 2.

Three cases were diagnosed before the changes in WHO classification (0.025 cases per month) compared to 8 cases (1.143 cases per month) after the changes. This corresponded to a 45-fold increased risk of being diagnosed with AVL after the change in WHO classification compared to before ($P < .001$; CI95%:10.88-265.31).

The mean age of all included patients was 67 years. Patients diagnosed after the changes in WHO diagnosis were in average more than 20 years older than patients diagnosed in the early period ($P < .05$). The majority of patients presented with large, ecchymotic plaques while patients diagnosed prior to the WHO changes presented with nodules, leading to a significantly smaller lesion size before the WHO changes ($P < .05$).

Patients diagnosed with AVL received different treatment over the years. Seven patients had no treatment of which 4 were planned for yearly follow-up with PET/CT scan, one had the lesion removed and 3 patients (28%) were recommended mastectomy, of whom 2 abstained due to heart failure and doubt concerning surgery (Table 1).

Patients were followed for in average 22 month after AVL diagnosis (6- 104 months). None developed AS during follow-up.

Discussion

We found a more that 45-fold increased risk of AVL diagnosis after change in WHO classification. Due to the increasing incidence of breast cancer in Denmark and the extended use of breast conserv-

Please cite this article as: Nanja Gotland et al, Radiation Induced Atypical Vascular Lesion in the Breast, Clinical Breast Cancer, https://doi.org/10.1016/j.clbc.2022.08.010

ing surgery with radiotherapy, an increase in radiotherapy induced AVL is expected. According to the yearly Danish national quality assessment report, the number of breast cancer patients receiving radiotherapy increased by 12% from 2012 to 2018.[11] This can only explain a very small part of the increase in the AVL diagnosis. The main increase is supposed to be due to an increased awareness due to the change in diagnosis to a specific diagnosis of AVL compared a previous lack of consensus and thus more descriptive reports.

Patients in the current study were generally older, compared to previous studies on AVL performed before the change in the WHO classification.[7,8] Similar younger age was found in patients diagnosed in the early period of our study while women diagnosed after the changes of classification were older. This could be explained by the increasing age of breast cancer patients in general[12] and the more widespread use of breast conserving therapy and radiotherapy in elderly breast cancer patients. Due to this, an increasing age of patients with AVL could be expected in the future.

In the current study, none of the 11 patients developed AS. Most previously reported data on outcome favors a benign behavior of AVL but rare cases of AS developing from AVL have been reported[4,7] and large excisions are recommended.[8,9] In our case, where the majority of patients had large AVL in plaque formation, 1/3 of the patients were recommended mastectomy. The average age in our study was high and patients expected to be frailer with a higher degree of comorbidity, not making extensive surgery an appealing choice.

Due to the rarity of AVL we could only include 11 patients in our study. Only few, small studies exist on the behavior of AVL, the largest including 42 patients.[4] Larger studies with long follow-up are needed to clarify the clinical consequences of the increase in post radiation AVL and whether AVL has the potential to transform into AS or could safely be treated conservatively. Accordingly, a prospective study with surveillance with clinical examination, PET/CT scans and biopsy at clinical progression has been initiated at our department.

Conclusion

After the changes in the WHO classification the number of patients diagnosed with AVL has increased significantly. None of our patients developed AS in the short follow-up period. Patients were found to be older with expected poorer general health and frailty. Still, some of these patients are recommended extensive surgery despite the lack of evidence on benefit from the procedure. More evidence is needed on active surveillance without surgery of these patients to verify the benign nature of the disease to spare elderly frail patients extensive surgery in the future.

Disclosure

The authors have no conflicts of interest to declare

Reference

1. World Health Organisation classification of tumors of the breast, 5th Edition, (2019), IARC Press, p. 195-196. ISBN-13.
2. Patton KT, Deyrup AT, Weiss SW. Atypical vascular lesions after surgery and radiation of the breast: a clinicopathologic study of 32 cases analyzing histologic heterogeneity and association with angiosarcoma. *Am J Surg Pathol*. 2008;32:943–950.
3. Brenn T, Fletcher CD. Postradiation vascular proliferations: an increasing problem. *Histopathology*. 2006;48:106–114.
4. Brenn T, Fletcher CD. Radiation-associated cutaneous atypical vascular lesions and angiosarcoma. Clinicopathologic analysis of 42 cases. *Am J Surg Pathol*. 2005;29:983–996.
5. Fineberg S, Rosen P. Cutaneous angiosarcoma and atypical vascular lesions of the skin and breast after radiation therapy. *Am J Clin Pathol*. 1994;102:757–763.
6. Fraga-Guedes C, Gobbi H, Mastropasqua MG, et al. Clinicopathological and immunohistochemical study of 30 cases of post-radiation atypical vascular lesion of the breast. *Breast Cancer Res Treat*. 2014;146:347–354.
7. Gengler C, Coindre JM, Leroux A, et al. Vascular proliferations of the skin after radiation therapy for breast cancer; clinicopathologic analysis of a series in favor of a benign process. *Cancer*. 2007;109:1584–1598.
8. Ronen S, Ivan D, Torres-Cabala CA, et al. Post-radiation vascular lesions of the breast. *J Cutan Pthol*. 2019;46:52–58.
9. Yang Y, Vandergriff T, Nijhawan R. Surgical management of radiation-associated atypical vascular lesions. *Derm Surg*. 2018;44:1030–1033.
10. Bjerregaard B, Larsen OB. The Danish Pathology Register. *Scand J Public Health*. 2011;39(7):72–74 Suppl.
11. www.DBCG.DK/Kvalitetsindikatorrapport for Brystkræft 2020.
12. Varghese F, Wong J. Breast Cancer in the Elderly. *Surg Clin N Am*. 2018;98(4):819–833. doi:10.1016/j.suc.2018.04.002.

Please cite this article as: Nanja Gotland et al, Radiation Induced Atypical Vascular Lesion in the Breast, Clinical Breast Cancer, https://doi.org/10.1016/j.clbc.2022.08.010