Benign Vascular Proliferations in Irradiated Skin

Luis Requena, M.D., Heinz Kutzner, M.D., Thomas Mentzel, M.D., Rafael Durán, M.D., and José Luis Rodríguez-Peralto, M.D.

Several types of cutaneous vascular proliferations have been described in areas of irradiated skin, including both benign lesions, such as benign lymphangiomatous papules, atypical vascular lesions, or benign lymphangioendothelioma, and malignant neoplasms such as high-grade angiosarcomas. This report describes the clinicopathologic features of 15 cases of different types of benign cutaneous vascular proliferations arisen within irradiated skin. All patients were female ranging in age from 33 to 72 years, and they had received postoperative external radiotherapy for treatment of breast carcinoma (14 cases) or ovarian carcinoma (one case). In those cases in which the latency interval period between radiotherapy and the development of the vascular lesion was known from the clinical records, the latency interval period elapsed between radiotherapy and diagnosis of the vascular lesion ranged from 3 to 20 years. The most common clinical presentation of the cutaneous lesions consisted of papules, small vesicles, or erythematous plaques on the irradiated field. Histopathologically, most lesions consisted of irregular dilated vascular spaces, with a branching and anastomosing pattern, thin walls, and lymphatic appearance involving the superficial dermis. A discontinuous single layer of endothelial cells with flattened nuclei lined these vascular channels, and numerous small stromal papillary formations also lined by endothelial cells projected into the lumina of the dilated lymphatic vessels. These cases were classified as benign lymphangiomatous papules or plaques. Two cases showed different histopathologic findings because they consisted of poorly circumscribed and focally infiltrating irregular jagged vascular spaces involving the entire dermis and lined by inconspicuous endothelial cells. In some areas these irregular slit-like vascular spaces dissected collagen bundles of the dermis. These cases were classified as atypical vascular proliferations mimicking benign lymphangioendothelioma or patch-stage Kaposi’s sarcoma. All cases showed similar immunohistopathologic differential diagnosis. Key Words: Benign lymphangiomatous papules—Atypical vascular proliferations—Benign lymphangioendothelioma—Kaposi’s sarcoma—Angiosarcoma—Radiotherapy.


The occurrence of vascular proliferations arisen in previously irradiated areas of the skin is well known. These cutaneous vascular proliferations after radiotherapy include both benign lesions, such as benign lymphangiomatous papules,1,10,13,15,21,22,25,27,28,30,38,40,55 atypical vascular lesions,12 or benign lymphangioendothelioma (also named acquired progressive lymphangioendothelioma),44 and malignant neoplasms such as high-grade angiosarcomas.2,3,5,7,9,11,12,16,17,20,31,34–37,39,45–47,49 These vascular lesions appear within the field of radiation therapy, and the latency interval time elapsed between radiotherapy and the onset of the cutaneous lesions is usually of several years. Some of the benign lesions, such as atypical vascular proliferations12 and benign lymphangioendothelioma,44 may mimic histopathologically patch-stage Kaposi’s sarcoma or well-differentiated angiosarcoma and thus may cause problems in the histopathologic differential diagnosis.

In this study 15 patients with several types of benign vascular proliferations arisen within the area of irradiated skin were investigated from clinical, histopathologic, and immunohistochemical standpoints. Benign lymphangiomatous papules and plaques were the most common lesions. Prominent intravascular papillary projections lined by endothelial cells were seen in some of the dilated lymphatic vessels. Other patients showed more atypical vascular proliferations mimicking benign lymphangioendothelioma, patch-stage Kaposi’s sarcoma, or Dabska’s tumor in miniature. This report expands the
MATERIALS AND METHODS

Fifteen cases of cutaneous vascular proliferations arisen in areas of previously irradiated skin were retrieved from the files of Dermatohistopathologisches Gemeinschaftslabor, Friedrichshafen, Germany (10 cases), the Department of Dermatology, Fundación Jiménez Díaz, Universidad Autónoma, Madrid, Spain (three cases), the Department of Pathology, Hospital 12 de Octubre, Universidad Complutense, Madrid, Spain (one case), and the Department of Pathology, Hospital de Elda, Alicante, Spain (one case). Clinical information was obtained from the hospital records or laboratory request forms. The following data were recorded, if available, for each patient: age, sex, primary disease, time latency interval elapsed between radiotherapy and diagnosis of the vascular lesion, clinical appearance, and location of the lesions. Where possible, follow-up information was obtained from the laboratory request forms and referring dermatologists or pathologists.

For conventional light microscopy, tissue was fixed in 4% formalin, embedded in paraffin wax, and cut and stained with hematoxylin and eosin. For immunohistochemical studies representative sections of 10 cases were examined by the alkaline phosphatase anti-alkaline phosphatase technique using appropriate positive and negative controls throughout. Automated immunostaining was performed on a BioTek Solutions Tech Mate (TechMate 500, Biotech Solutions, Dako, Glostrup, Denmark). The following antibodies were used: CD31 (JC/70A, 1:30, Dako, Hamburg, Germany), CD34

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (y)/sex</th>
<th>Primary disease</th>
<th>Latency interval (y)*</th>
<th>Clinical presentation</th>
<th>Site</th>
<th>Treatment</th>
<th>Histopathologic findings</th>
<th>Follow-up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72/F</td>
<td>Breast carcinoma</td>
<td>20</td>
<td>Two papules</td>
<td>Axillary fold</td>
<td>Local excision</td>
<td>BLAPa</td>
<td>NERM 6 mo after diagnosis</td>
</tr>
<tr>
<td>2</td>
<td>—</td>
<td>Breast carcinoma</td>
<td>10</td>
<td>Two papules</td>
<td>Chest wall</td>
<td>Local excision</td>
<td>BLAPa, nodular lymphocytic infiltrates</td>
<td>NERM 13 y after diagnosis</td>
</tr>
<tr>
<td>3</td>
<td>64/F</td>
<td>Breast carcinoma</td>
<td>—</td>
<td>Single papule</td>
<td>Chest wall</td>
<td>Local excision</td>
<td>BLAPa, nodular lymphocytic infiltrates</td>
<td>NERM 5 y after diagnosis</td>
</tr>
<tr>
<td>4</td>
<td>44/F</td>
<td>Breast carcinoma</td>
<td>—</td>
<td>Erythematous plaque</td>
<td>Chest wall</td>
<td>Local excision</td>
<td>BLAPI</td>
<td>NERM 4 y after diagnosis</td>
</tr>
<tr>
<td>5</td>
<td>49/F</td>
<td>Breast carcinoma</td>
<td>—</td>
<td>Several papules</td>
<td>Chest wall</td>
<td>Local excision</td>
<td>BLAPI</td>
<td>NERM 3 y after diagnosis</td>
</tr>
<tr>
<td>6</td>
<td>62/F</td>
<td>Breast carcinoma</td>
<td>11</td>
<td>Several papules</td>
<td>Chest wall</td>
<td>Local excision</td>
<td>BLAPI in upper areas, atypical vascular proliferation in deeper areas</td>
<td>NERM 3 y after diagnosis</td>
</tr>
<tr>
<td>7</td>
<td>62/F</td>
<td>Breast carcinoma</td>
<td>6</td>
<td>Several papules</td>
<td>Chest wall</td>
<td>Local excision</td>
<td>BLAPa</td>
<td>NERM 2 y after diagnosis</td>
</tr>
<tr>
<td>8</td>
<td>61/F</td>
<td>Ovarian carcinoma</td>
<td>—</td>
<td>Erythematous plaque with overlying papular lesions</td>
<td>Inguinal area</td>
<td>Local excision</td>
<td>BLAPa</td>
<td>NERM 1 y after diagnosis</td>
</tr>
<tr>
<td>9</td>
<td>33/F</td>
<td>Breast carcinoma</td>
<td>3</td>
<td>Single papule</td>
<td>Chest wall</td>
<td>Local excision</td>
<td>BLAPI</td>
<td>NERM 6 mo after diagnosis</td>
</tr>
<tr>
<td>10</td>
<td>44/F</td>
<td>Breast carcinoma</td>
<td>—</td>
<td>Single papule</td>
<td>Chest wall</td>
<td>Local excision</td>
<td>BLAPI</td>
<td>NERM 6 y after diagnosis</td>
</tr>
<tr>
<td>11</td>
<td>70/F</td>
<td>Breast carcinoma</td>
<td>4</td>
<td>Single papule</td>
<td>Chest wall</td>
<td>Local excision</td>
<td>Atypical vascular proliferation with endothelial tufts</td>
<td>NERM 5 y after diagnosis</td>
</tr>
<tr>
<td>12</td>
<td>54/F</td>
<td>Breast carcinoma</td>
<td>12</td>
<td>Single papule with appearance of dermatofibroma</td>
<td>Chest wall</td>
<td>Local excision</td>
<td>Atypical vascular proliferation</td>
<td>NERM 2 y after diagnosis</td>
</tr>
<tr>
<td>13</td>
<td>68/F</td>
<td>Breast carcinoma</td>
<td>10</td>
<td>Single papule</td>
<td>Chest wall</td>
<td>Local excision</td>
<td>BLAPa</td>
<td>NERM 4 y after diagnosis</td>
</tr>
<tr>
<td>14</td>
<td>67/F</td>
<td>Breast carcinoma</td>
<td>6</td>
<td>Erythematous plaque</td>
<td>Chest wall</td>
<td>Local excision</td>
<td>Biopsy BLAPI</td>
<td>NERM 1 y after diagnosis</td>
</tr>
<tr>
<td>15</td>
<td>58/F</td>
<td>Breast carcinoma</td>
<td>14</td>
<td>Single pedunculated lesion</td>
<td>Chest wall</td>
<td>Local excision</td>
<td>BLAPa in upper areas, atypical vascular proliferation in deeper areas</td>
<td>NERM 1 y after diagnosis</td>
</tr>
</tbody>
</table>

* Latency interval refers to the time elapsed between radiotherapy and diagnosis of the vascular lesion. BLAPa, benign lymphangiomatous papule; BLAPI, benign lymphangiomatous plaque; NERM, no evidence of recurrence or metastatic disease.
RESULTS

Clinical Findings

Table 1 summarizes the clinical data of the 15 patients. Briefly, all of them were female. Fourteen patients had a history of breast carcinoma, and one (case no. 8) had an ovarian carcinoma. Age range of the patients was 33–72 years (median 52 years). All patients with breast carcinoma underwent partial or radical mastectomy, and an ovarian carcinoma was excised in case no. 8. All patients received postoperative external radiotherapy. In those cases in which the latency interval period between radiotherapy and the development of the vascular lesion was known from the clinical records (10 cases), the latency interval period elapsed between radiotherapy and diagnosis of the vascular lesion ranged from 3 to 20 years (median 9 years). All lesions were located on the anterior chest wall, except those of the case no. 8, who received radiotherapy for ovarian carcinoma and the cutaneous lesions appeared on the inguinal area. The most common clinical presentation of the cutaneous lesions consisted of papules, small vesicles, or erythematous plaques on the irradiated field (Fig. 1). Case no. 12 showed a single papule that was clinically considered as dermatofibroma.

FIG. 1. Clinical appearance of the lesions. (A) Papules or small vesicles. (B) Erythematous plaques on the irradiated field.

FIG. 2. Case no. 1. (A) A dome-shaped, exophytic lesion projecting over the skin surface in a case of benign lymphangiomatous papule. (B) Irregular dilated vascular spaces, with a branching and anastomosing pattern, thin walls, and lymphatic appearance, were seen in the superficial dermis. (C) A discontinuous single layer of endothelial cells with spindled or flattened nuclei lined these vascular channels and their lumina appeared empty. (D, E, and F) Immunohistochemical demonstration of CD31 immunoreactivity of endothelial cells lining the vascular structures. (G, H, and I) Immunohistochemical study for α-smooth muscle actin antibody demonstrated that the dilated vessels lacked a peripheral ring of actin-positive pericytes. Note the actin-positive internal control of the smooth muscle fibers of the arrector pili muscle in the deeper dermis in G and the walls of the adjacent capillary blood vessels containing erythrocytes within their lumina.
Only one patient (case no. 3) showed clinical evidence of lymphedema in the left arm. In all cases the lesions were removed by local excision. In each patient a single lesion was histopathologically studied, except case no. 2 with two lesions excised and case no. 8 from whom five lesions were removed. Follow-up ranged from 0.5 to 13 years (median 3.4 years), and none of the patients developed recurrent lesions or metastatic disease.

**Histopathologic Features**

At low power all lesions appeared as relatively well-circumscribed vascular proliferations involving the der-
mis, without extension to the subcutaneous fat. The epidermis was normal. Eight lesions presented as dome-shaped, exophytic papules projecting over the skin surface (case nos. 1–3, 6–8, 13, and 15) (Fig. 2) and the other seven cases (case nos. 4, 5, 9–12, and 14) were flat with a plaque-like morphology (Fig. 3). In most lesions (case nos. 1–10 and 13–15), irregular dilated vascular spaces, with a branching and anastomosing pattern, thin walls, and lymphatic appearance, were seen in the superficial dermis (Figs. 2 and 3). A discontinuous single layer of endothelial cells with spindled or flattened nuclei lined these vascular channels and their lumina appeared empty. In many areas adjacent vascular channels showed a “back-to-back” arrangement, with the two vascular lumina separated only by a thin layer of endothelial cells. Numerous small papillary projections, also lined by a single layer of endothelial cells, projected into the lumina of the dilated lymphatic vessels. The papillary projections were especially prominent in case no. 13 (Fig. 4). The stroma of the lesions consisted of fibrillary collagen, numerous spindled or stellate fibroblasts, and in some cases abundant deposits of interstitial mucin between the dilated vascular channels. Two cases (case nos. 2 and 3) showed dense nodular infiltrates of lymphocytes with germinal centers in the vicinity of the dilated vascular channels (Fig. 5). The stroma of one of the lesions of case no. 8 showed striking metaplasia of mature adipocytes intermingled with the dilated vascular spaces (Fig. 6). All these cases were classified as benign.

FIG. 4. Case no. 13. (A) A benign lymphangiomatous papule showing an exophytic and pedunculated morphology with prominent intravascular papillary formations. (Large arrow indicates the area enlarged in B and C. Small arrow indicates the area enlarged in D and E). (B, C, D, and E) In some areas prominent papillary projections of endothelial cells protruded within the lumina of the dilated lymphatic vessels.

FIG. 5. Case no. 2. (A) A benign lymphangiomatous papule with dense nodular infiltrates of lymphocytes in the stroma. (B) Irregular dilated vascular channels with lymphatic appearance. (C) Dense nodular infiltrates of lymphocytes close to the dilated lymphatic vessels.
lymphangiomatous papules or benign lymphangiomatous plaques.

Two lesions (case nos. 11 and 12) showed different histopathologic findings. They consisted of poorly circumscribed and focally infiltrating irregular jagged vascular spaces involving the entire dermis, lined by inconspicuous endothelial cells. In some areas these irregular slit-like vascular spaces dissected collagen bundles of the dermis. Erythrocytes were not seen in the lumina of the vascular channels, and a few lymphocytes were present in the stroma. Case no. 11 also showed conspicuous tufts of endothelial cells protruding into the lumens of neofomed vessels. These striking endothelial tufts resembled those of Dabska's tumor in miniature, although in contrast with authentic Dabska's tumor, the endothelial tufts of this lesion had no connective tissue core and they were grape-like papillary formations exclusively composed of endothelial cells. Therefore, we classified this lesion as atypical vascular proliferation with dabskoid features (Fig. 7). Case no. 12 showed irregular jagged vascular spaces dissecting collagen bundles of the dermis and abundant interstitial hemosiderin deposits, mimicking patch-stage Kaposi's sarcoma (Fig. 8). Case nos. 6 (Fig. 9) and 15 combined features of benign lymphangiomatous papules in the upper dermis and atypical vascular proliferations with focally infiltrative pattern in deeper dermis.

Immunohistochemical Findings

All cases showed similar immunohistochemical findings. Endothelial cells lining the vascular spaces expressed immunoreactivity for CD31, but they stained only focally positive for CD34 or were negative for this marker. Although a few vessels showed an attenuated muscle layer stained for α-smooth muscle actin antibody surrounding the endothelial cells, this marker was essentially negative in most vascular structures. Ki67 stained some keratinocytic nuclei of the epidermal basal layer, but it was negative in the nuclei of the endothelial cells lining the vascular structures.

DISCUSSION

The histopathologic characteristics of these cases of vascular proliferations arisen in irradiated skin were those of lymphatic vessels because they consisted of dilated vascular spaces with thin walls lined by a single discontinuous layer of flat endothelial cells and arranged in a "back-to-back" fashion. Furthermore, the immunohistochemical profile of the endothelial cells lining the neofomed vessels, which expressed immunoreactivity for CD31, but not for CD34, and the absence of a periphereral ring of actin-positive pericytes, also supports a lymphatic nature for these neofomed vessels. Benign lymphangiomatous papules and plaques seem to be the most common vascular lesions developed in areas of irradiated skin. They have been erroneously named “lymphangioma circumscriptum” by some authors, but this is an inaccurate term because lymphangioma circumscriptum refers to localized malformations of lymphatic vessels of the superficial dermis. Benign lymphangiomatous papules and plaques are the lymphatic counterpart of telangiectases, and they result from acquired permanent dilatation of lymphatic capillaries. They may appear in areas of skin affected by obstruction...
or destruction of the lymphatic drainage and have been described as a result of interference of lymphatic vessels secondary to radiotherapy or surgery. Benign lymphangiomatous papules and plaques, however, may also appear in the skin of elderly persons without any evidence of secondary lymphatic damage. Clinically, benign lymphangiomatous papules arisen in areas of irradiated skin appear as multiple, persistent, translucent, thick-walled, whitish vesicles or small papules. Some lesions may have polypoid shape and punctum provokes the flow of a milky liquid. Benign lymphangiomatous plaques appear as erythematous flat areas of indurated skin. Histopathologically, both lesions consist of dilated lymphatic vessels positioned within papillary dermis, although some dilated lymphatic vessels may also be seen involving the reticular dermis. The lumina of the dilated vessels show no contents or are filled by homogeneous eosinophilic material, and they are lined by a thin wall composed of a single discontinuous layer of endothelial cells. A striking histopathologic feature in our cases consisted of the presence of prominent papillary projections of stroma lined by endothelial cells or tufts of endothelial cells without stroma axis protruding within the lumina of the dilated lymphatic vessels. These intravascular papillary projections have been previously described in vascular proliferations of irradiated skin as well as in lymphatic malformations, and they are interpreted as the lymphatic counterpart of Masson’s intravascular papillary endothelial hyperplasia.

The cases of this series classified as atypical vascular proliferations showed histopathologic similarities with benign lymphangioendothelioma, also named acquired progressive lymphangioma, and with patch-stage Kaposi’s sarcoma. Indeed, a case of acquired progressive lymphangioma of the skin after radiotherapy has been previously described, although this case more likely represents an example of postirradiation atypical vascular proliferation. Benign lymphangioendothelioma is a rare lymphatic neoplasm originally described by Wilson Jones et al. Approximately 40 cases of this uncommon neoplasm have been reported in the literature. Clinically, lesions of benign lymphangioendothelioma appear as a solitary reddish or bruise-like slowly growing plaque that does not have a site of predilection. Histopathologically, benign lymphangioendothelioma is composed of delicate, thin-walled, endothelium-lined dilated vascular spaces involving the superficial dermis. In some areas intravascular papillary stromal projections are present, resembling papillary endothelial hyperplasia. As the lesion descends within deeper dermis, the vascular spaces collapse and dissect the collagen bundles, mimicking patch-stage Kaposi’s sarcoma, especially the lymphangioma-like variant of Kaposi’s sarcoma, and well-differentiated angiosarcoma. Preexisting vessels and adnexal structures of the dermis also appear dissected by the neofomed vascular channels. These vascular spaces appear empty or to contain proteinaceous material. Erythrocytes and hemosiderin deposits are characteristically absent. The endothelial cells in the les-
sional vessels are present in greater numbers than in normal lymphatic channels, and in some places they are crowded together. However, no nuclear atypia is found in the endothelial cells lining the cleft-like vessels. In contrast with patch-stage Kaposi’s sarcoma, lesions of benign lymphangioendothelioma show no erythrocytes or hemosiderin deposits, and there are no plasma cells in the stroma. With the exception of the case reported by Rosso et al., which probably is better interpreted as an example of postradiotherapy atypical vascular proliferation, no other examples of benign lymphangioendothelioma have been reported in irradiated skin. To the best of our knowledge, the striking tufts of endothelial cells, seen in our case no. 11, which protruded within the irregular jagged vascular channels resembling the features of Dabska’s tumor in miniature, have not been previously described in the vascular proliferations arisen in irradiated skin. Case no. 12 showed irregular jagged vascular channels and abundant hemosiderin deposits in the stroma, mimicking patch-stage Kaposi’s sarcoma. However, in contrast with authentic Kaposi’s sarcoma, the so-called promontory sign that results from the dissection of preexisting capillaries by the proliferating endothelial cells and an inflammatory infiltrate of plasma cells were not seen in case no. 12.

Histopathologic differential diagnosis between the atypical vascular proliferations in areas of irradiated skin also includes well-differentiated angiosarcoma. In contrast with angiosarcoma, atypical vascular proliferations in irradiated skin do not involve the subcutaneous tissue, and there is not substantial cytologic atypia because the nuclei of endothelial cells lining the vascular channels are monomorphous, with inconspicuous nucleoli and no mitotic figures. Another frequent histopathologic finding in angiosarcoma consists of the presence of multilayering of atypical endothelial cells lining irregular vascular and anastomosing channels, the so-called piling-up phenomenon, and this feature is not seen in atypical vascular proliferations in irradiated skin. Usually, many nuclei of neoplastic endothelial cells of angiosarcoma express proliferation markers such as Ki67, and this marker was essentially negative in our cases. Furthermore, there is not evidence that these atypical vascular proliferations represent premalignant lesions for the development of postirradiation angiosarcoma, and the follow-up of our patients has demonstrated that these lesions have a benign biologic behavior.

In summary, vascular proliferations arisen in areas of irradiated skin comprise a wide spectrum of lesions. The most common lesions are benign lymphangiomatous papules and plaques, but more atypical vascular proliferations resembling benign lymphangioendothelioma, patch-stage Kaposi’s sarcoma, and well-differentiated angiosarcoma may also appear. All these vascular lesions arise within the field of irradiated skin and usually appear after a latent period of several years after radiotherapy. Although these vascular proliferations in irradiated skin may raise problems in the histopathologic differential diagnosis with malignant vascular proliferations, they invariably show a benign biologic behavior.

REFERENCES


