Poromas with *YAP1–MAML2* fusions in a poromatosis case

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INTRODUCTION

Eccrine poromatosis is a rare condition characterized by multiple eccrine poromas, most commonly following multidrug chemotherapy and/or irradiation for malignant tumors.[1] Notably, a recent study revealed the frequent presence of yes-associated protein 1 (*YAP1*) fusions, including *YAP1*-mastermind-like transcriptional coactivator 2 (*MAML2*) and *YAP1*-nut midline carcinoma family member 1 (*NUTM1*), in sporadic poromas.[2] Here, we describe a patient with multiple poromas following breast cancer treatment and determine whether the poromas harbor *YAP1* fusions through immunohistochemical and molecular analyses.

CASE REPORT

A 58-year-old Japanese woman presented with a 2-year history of slow-growing cherry-colored lesions on her back (12 × 7 and 4 × 3 mm in size), right upper arm (5 × 3 mm), and right aspect of the abdomen (6 × 4 mm) (Fig 1). The largest nodule appeared at the age of 56, and the other 3 developed consecutively over 2 years. The 4 tumors initially appeared as pinpoint-sized, red lesions. Owing to a previous history of breast carcinoma, the patient underwent left mastectomy and chemotherapy with cyclophosphamide, doxorubicin, and paclitaxel at the age of 46. No recurrence has been observed since then.

Histologic examination of the 4 lesions confirmed the diagnosis of poromas following excisional biopsies. The tumors consisted of small, uniform, basophilic, poroid cells with occasional intracytoplasmic lumina and ductal structures. The tumors were connected to the epidermis, extending toward the dermis, forming broad anastomosing bands (Fig 2, *A* and *B*). There was no cellular atypia. Two years after the initial excision, the patient revisited our hospital with 4 new papules on the trunk and left calf that had appeared 1 year before on the right aspect of the chest (2 × 2 and 1.5 × 1.5 mm in size), left aspect of the chest (5 × 4 mm), and the left calf (8 × 3 mm) (Fig 1). The clinical and histologic characteristics were similar to those of the resected lesions.

To examine the role of *YAP1* fusions in the development of multiple poromas, we performed *YAP1* immunohistochemical staining of the 8 poromas, as previously described.[2] Staining using an anti-N-terminal region antibody, which recognizes both wild-type *YAP1* and poroma-related *YAP1* fusions, showed nuclear expression in all 8 lesions (Fig 2, *C*). Conversely, an anti-C-terminal region antibody, which reacts with wild-type *YAP1* but not *YAP1* fusions, showed negative staining in all lesions (Fig 2, *D*). No lesions expressed *NUTM1* using clone *C52B1*.

Next, we performed reverse transcription-polymerase chain reaction using ribonucleic acid extracted from paraffin sections of the 8 poromas to determine the expression of specific *YAP1* fusions (Fig 3, *A*). The analysis identified *YAP1* exon

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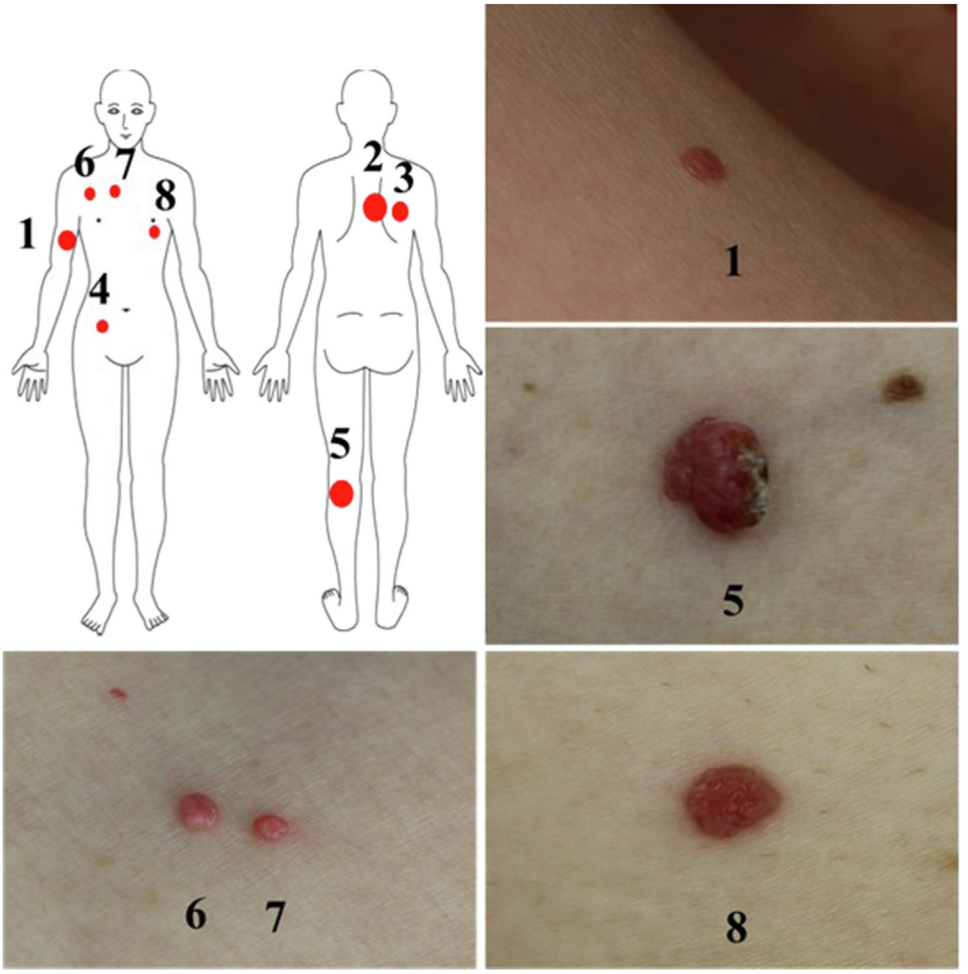

Fig 1. Asymptomatic tumors on the trunk and extremities. #1 to #4, which had developed at the age of 58 years, and #5 to #8, which had developed at the age of 60 years, were resected.

5/6—*MAML2* fusions in 6 lesions, and the remaining 2 lesions expressed *YAP1* exon 1—*MAML2* fusion. Six poromas co-expressed reciprocal *MAML2—YAP1* fusions.

DISCUSSION

Since Goldner[3] first reported a patient with eccrine poromatosis in 1970, more than 20 cases have been described in the English literature.[4] Nineteen of these received multidrug chemotherapy for hematologic malignancies or solid cancers.[4] Their onset period ranged from 6 months to 18 years after cancer diagnosis.[4] Several to more than 100 poromas occurred in 1 individual, and half of the lesions developed on the palms and soles.[1] Except for palmoplantar lesions, our case presented as typical eccrine poromatosis with an onset 10 years after breast cancer treatment.

YAP1 is a transcriptional coactivator that binds to the transcription factor TEA domain family member (TEAD), inducing the production of proteins involved in cell proliferation.[5] *YAP1* is distributed in the cytoplasm under steady-state conditions while maintaining a balance between production and disassembly and avoids decomposition by translocating to the nucleus.[6] In our case, immunohistology for the N-terminal region of *YAP1*, which includes TEAD-binding residues,[7] revealed positive poroma nuclei. This localization indicates that the protein contributes to the continuous cell division of poromas.[2] *MAML2* is a nuclear protein that promotes cell proliferation through the Notch signaling pathway.[8] *NUTM1* is a protein involved in spermatogenesis.[8]

YAP1 fusions are abnormal gene rearrangements mainly found in cancers,[7] including porocarcinoma.[2] Fifty-four percent of porocarcinomas have *YAP1—NUTM1* fusions, and 9% harbor *YAP1—MAML2* fusions.[2] YAP1—NUTM1 fusions have attracted attention in oncogenesis research because porocarcinomas with *YAP1—NUTM1* fusions present more aggressive histologic features than those with *YAP1—MAML2* fusions.[9]

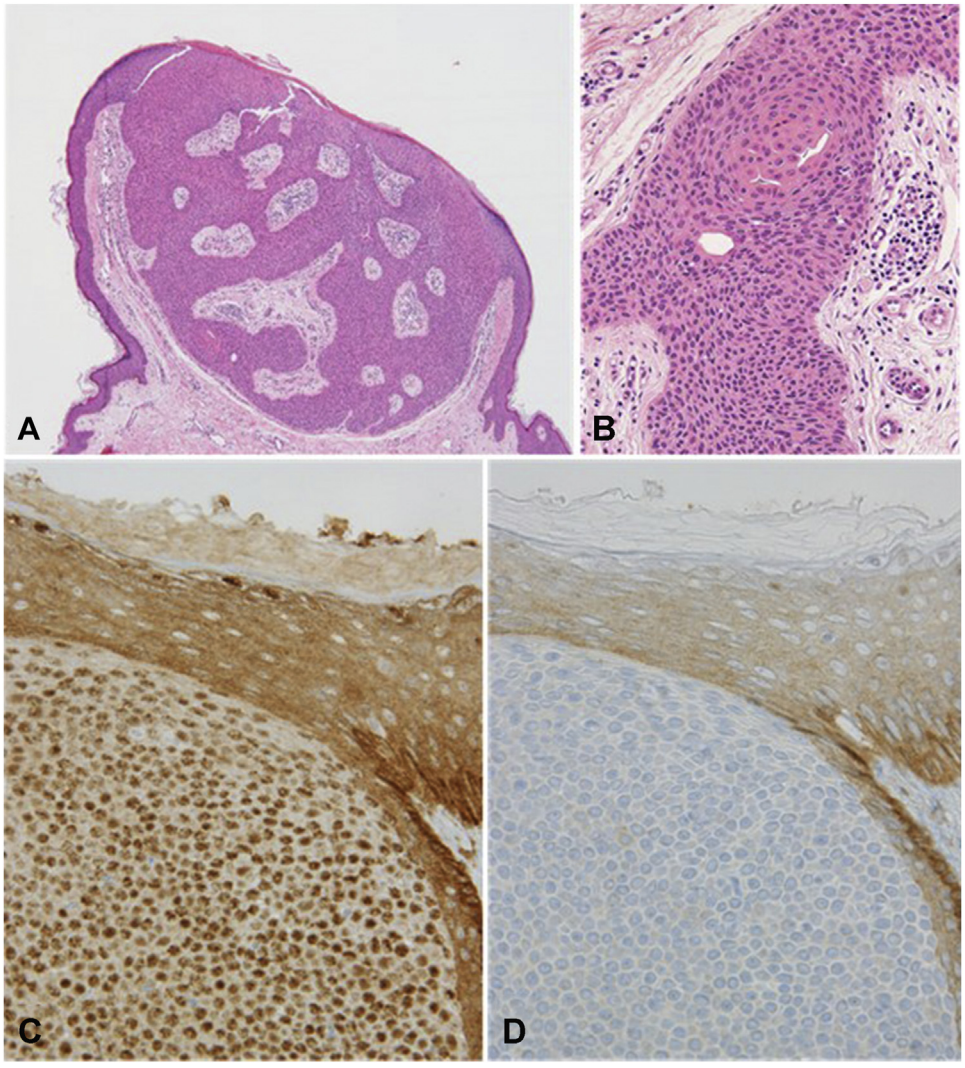

Fig 2. Skin excision of papule #6. **A,** Hematoxylin-eosin staining (original magnification: ×40). **B,** hematoxylin-eosin staining (original magnification: ×200). **C,** YAP1 N-terminal immunostaining (clone 2F12, original magnification: ×400). **D,** YAP1 C-terminal immunostaining (clone D8H1X-XP, original magnification: ×400). Positive YAP1 N-terminal staining of poroma nucleoli (**C**). Keratinocytes around the tumor showed diffusely positive cytoplasmic staining for YAP1 (**C** and **D**) and were free of *YAP1* rearrangement. Negative C-terminal staining of poromas (**D**) indicated that no functional protein was produced by *MAML2*−*YAP1* fusions.

Surprisingly, the benign counterparts of porocarcinomas, poromas, were also found to have recurrent YAP1 fusions; 71 of 104 sporadic poromas had *YAP1*−*MAML2* fusions, and 21 harbored *YAP1*−*NUTM1* fusions.[2] In our case, all 8 poromas harbored *YAP1*−*MAML2* fusions. Although there is no clear evidence that *YAP1*−*NUTM1* fusions promote malignant transformation in preexisting poromas, the near absence of these fusions might lead to a better prognosis. The monoclonal antibody against *NUTM1* has 100% specificity and 87% sensitivity.[10] Therefore, a combination of immunohistochemical staining with reverse transcription-polymerase chain reaction or fluorescent in situ hybridization would be optimal for completely excluding the existence of *YAP1*−*NUTM1* fusions.[10] It is necessary to investigate whether other eccrine poromatosis cases have only *YAP1*−*MAML2* fusions, which may explain why *de-novo* porocarcinomas have not been reported in eccrine poromatosis.[1,4]

YAP1−*MAML2* fusions occur by intrachromosomal inversion. Specifically, in the long arm of chromosome 11, *YAP1* and *MAML2* break, flip 180 degrees, and fuse,[2,8] and *YAP1*−*MAML2* and

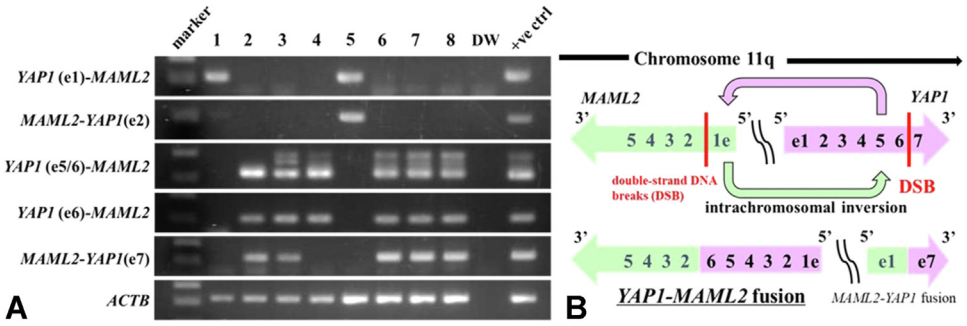

Fig 3. A, Detection of *YAP1* fusions by reverse transcription-polymerase chain reaction. #1 and #5 had *YAP1 (exon [e]1)—MAML2* fusion. #2, #3, #4, #6, #7, and #8 harbored *YAP1 (e5/6) —MAML2* fusion. The lane number matches that of the poromas shown in Fig 1. **B,** Schematic description of gene fusions: the process of *YAP1*(e5/6)—*MAML2* and reciprocal *MAML2—YAP1*(e7) fusion occurrence. *ACTB*, Beta-actin; *DW,* distilled water (negative control).

MAML2—YAP1 fusions develop reciprocally (Fig 3, *B*). A recent study showed 3 *YAP1—MAML2* fusion variations in 71 poromas according to the point at which YAP1 breaks at introns 1, 5, and 6.[2] There are no significant clinical differences between poromas with these 3 variations.[2] The existence of 2 variants in our case suggests that 2 or more *YAP1—MAML2* fusion variants may occur when multiple poromas develop in a patient.

The trigger for *YAP1* fusions in poromas is double-strand DNA breaks[11] in tissue stem cells adjacent to the acrosyringium, which also occur in healthy individuals.[11] Anticancer agents, especially anthracycline antibiotics and platinum drugs, and irradiation exert their therapeutic effects by causing double-strand DNA breaks.[11] Therefore, these clastogens probably induce an increased frequency of gene rearrangements following DNA repair. In our case, the chemotherapeutic agent inducing double-strand DNA breaks was doxorubicin. The existence of *YAP1* fusions in multiple poromas supports the hypothesis that chemo/radiotherapy generates the relevant gene rearrangements.

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Conflicts of interest

None disclosed.

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