Acne inversa complicated by squamous cell carcinoma in association with diffuse malignant peritoneal mesothelioma arising in the absence of predisposing factors: a case report

Diffuse malignant peritoneal mesothelioma (DMPM) is a relatively rare neoplasm. Risk factors associated with its development include asbestos exposure, chronic irritation or inflammation of the peritoneum, abdominal radiotherapy, familial Mediterranean fever and simian virus 40. A familial segregation of this neoplasia has been reported in small villages of the Cappadocian region of Turkey, and it has been postulated that hereditary factors may predispose to mesothelioma, even with exposure to small amounts of asbestos. We report a case of DMPM, which apparently occurred in the absence of predisposing factors in a patient with a clinical history characterized by recurrent pre-sacral acne inversa of long duration. The association of this chronic inflammatory disease with DMPM has never been reported. The genetic locus for acne inversa has recently been identified within the 1p21.1–1q25.3 chromosomal region. Interestingly, frequent losses in chromosomal region 1p.21–22 have been found in mesothelioma as well. It is thus tempting to speculate that genetic mutations involving chromosome 1p.21–22 may account for the development of both diseases.


Recently, hereditary factors have also been claimed to be determinants of the apparent autosomal dominant transmission of malignant mesothelioma in families living in small villages of the Cappadocian region of Turkey. Hereditary factors seem to behave as cofactors with asbestos exposure in the pathogenesis of mesothelioma. Moreover, DMPM has been found in association with hereditary syndromes, such as Marfan and Ehlers-Danlos syndromes, and it has been speculated that genetic factors in these patients may predispose them to...
mesothelioma after exposure to even small amounts of asbestos.\textsuperscript{12}

We report herein a case of DMPM, which apparently occurred in the absence of predisposing factors.

Case report
A 47-year-old man was admitted to our hospital with ascites and abdominal pain. Paracentesis and subsequent cytologic examination of the ascitic fluid were performed, and in light of the cytologic findings, a peritoneal biopsy was also carried out.

The patient died 3 months after the diagnosis of DMPM was made. He was a physician employed in a hospital and neither exposure to asbestos nor chronic irritation or irradiation of the peritoneum was obtained in the history. The past clinical history was significant for recurrent acne inversa (Verneuil’s disease or suppurative hidradenitis) of greater than 25 years duration, arising during the post-pubertal period and involving the peri-anal skin. There was neither a history of diabetes mellitus nor alcoholism. The patient had undergone surgery 1 year prior to the appearance of the DMPM because of a squamous cell carcinoma complicating the acne inversa. Considering the family history, none of his family members had been exposed to asbestos. The 20-year-old son of the patient’s sister was also affected by acne inversa, whereas the patient’s father had died from a pulmonary carcinoma at 70 years of age.

This is the first case report of an association between DMPM and acne inversa.

Materials and methods

Tissue specimens
Surgical specimens of the cutaneous squamous cell carcinoma, removed 1 year prior to the diagnosis of DMPM, had been formalin fixed, paraffin embedded and subsequently cut into 5-\mu m sections for histologic diagnosis. An ascitic fluid cytologic smear was stained with Papanicolaou stain, and the sediment was stained with haematoxylin and eosin (H&E). Peritoneal fragments obtained at biopsy were fixed in 4\% buffered formalin and embedded in paraffin. Tissue sections 5 \mu m in thickness were then stained with routine H&E and submitted for immunohistochemical analysis in an attempt to verify the nature of the neoplastic cells.

Immunohistochemistry
Immunohistochemistry against calretinin (1 : 50 dilution; clone Dak-Calret1, Dakocytomation), carcino embryonic antigen (CEA) (1 : 50 dilution, clone II-7, Dakocytomation), epithelial membrane antigen

\begin{itemize}
\item \textbf{Results}
\end{itemize}

On macroscopic examination, the peri-anal squamous cell carcinoma presented as a 5 \times 4-cm ulcerated lesion (Fig. 1A). The microscopic appearance is shown in Fig. 1B. On the basis of the histologic findings, it was diagnosed as a well-differentiated, infiltrative squamous cell carcinoma with outer root sheath differentiation, i.e., a trichilemmal-type squamous cell carcinoma.

\textit{Fig. 1.} A) Macroscopic appearance of the pre-sacral squamous cell carcinoma developed on the surgical scar of acne inversa lesions. B) Histologic appearance of the squamous cell carcinoma. The presence of characteristic squamous cell nests (epithelial pearls) and the dermal infiltration aspects define the lesion as a well-differentiated, infiltrative squamous cell carcinoma with an outer root sheath differentiation (haematoxylin and eosin; original magnification \(\times 40\)).
Cytology of the ascitic fluid showed a very large number of mesothelial neoplastic cells with occasional lymphocytes and neutrophils. The mesothelial cells occurred singly and in large groups, including many papillary and spherical clusters (Fig. 2A), that were positively stained by calretinin and EMA antibodies.

Microscopic evaluation of the peritoneal biopsy samples disclosed tubulopapillary proliferation, composed of cells with eosinophilic cytoplasm, irregular pleomorphic nuclei, prominent nucleoli and infrequent mitoses (Fig. 2B).

Neoplastic cells were strongly labelled by calretinin (Fig. 2C), EMA (Fig. 2D) and cytokeratins 5/6, whereas no staining occurred with CEA. The neoplasm was therefore classified as a tubulopapillary DMPM.

Discussion

Acne inversa is a recurrent, chronic inflammatory disease that was initially described by Velpeau in 1833 as a peculiar process characterized by superficial abscesses in the axillae, under the breast and in the genitocrural and peri-anal areas. It was later named hidradenitis suppurativa by Verneuil, who ascribed the process to an inflammation of the sweat glands based merely on the anatomic distribution of the disease. More recently, on the basis of the histologic findings, it has been recognized as a disorder of the follicular epithelium leading to a subsequent follicular occlusion, occasional secondary apocrine involvement and follicular rupture with resultant inflammation and possibly secondary infection. Thus, the disease is currently defined by the more appropriate term acne inversa. We have described a case of acne inversa complicated by a squamous cell carcinoma in association with DMPM, which occurred in the absence of classic predisposing risk factors for mesothelioma.

Several authors have emphasized the co-occurrence of acne inversa and non-melanoma skin cancer. Even if it has not been fully clarified why acne inversa predisposes to cutaneous carcinoma, it has been postulated that chronic irritation and infection of long duration may lead to proliferative epidermal changes, including cancer. Thus, in the present case, the prolonged irritative stimulus may have accounted for the development of a squamous cell carcinoma at the site of acne inversa of 20 years duration.

In addition to cutaneous carcinoma, the high frequency of tumors other than those involving the skin among patients affected by acne inversa has also been highlighted. These neoplasias include buccal, primary liver, oesophageal, lung and kidney cancers, as well as haematopoietic neoplasias, whereas the association of acne inversa and mesothelioma has never been reported.

Given the frequent familial pattern of the disease, genetic factors have been thought to contribute to acne inversa with an autosomal dominant pattern of inheritance. Recently, the genetic locus responsible for acne inversa has been identified in a Chinese family at chromosome 1p21.1–1q25.3. Nevertheless, the width of this chromosomal region is not conducive to establishing the exact gene responsible for the disease with precision.

Fig. 2. A) Ascitic fluid sediment with a very large number of mesothelial cells, clustered in papillary and spherical structures and occasional lymphocytes and neutrophils (haematoxylin and eosin (H&E), original magnification ×400). B) Peritoneal biopsy fragments infiltrated by a neoplasia forming papillary structures and tubules (H&E, original magnification ×400). C) Neoplastic cells labelled by calretinin antibody (calretinin stain; original magnification ×200). D) Neoplastic cells labelled by EMA antibody (EMA stain, original magnification ×200).
Interestingly, frequent losses in chromosomal region 1p21–22 have been found in mesothelioma as well,25–28 and the gamma-glutamylcysteine ligase regulatory subunit gene that catalyses glutathione synthesis has been mapped to this region.27 Thus, it seems possible that genetic mutations at this region in acne inversa may compromise the anti-oxidant properties of cells, thus leading to a predisposition for the development of malignant tumors.

It is therefore tempting to speculate that in the present case, genetic alterations involving the 1p21–22 chromosomal region may account for the development of both acne inversa and DMPM. Furthermore, such a mutation may have been inherited by the nephew of the patient, who is exhibiting the initial manifestations of acne inversa.

In conclusion, acne inversa is an inflammatory syndrome that requires compulsive surveillance, so as to diagnose early and eventually prevent serious and life-threatening-associated neoplastic diseases. As this is the only reported case describing the association between acne inversa and DMPM, further epidemiologic studies are required to determine whether the association is coincidental or causally linked.

References
