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Case report

Thrombendarteriitis pulmonalis carcinomatosa Ceelen: an immunohistological investigation

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Summary. A 65-year-old woman died in sudden right heart failure caused by thrombendarteriitis pulmonalis carcinomatosa Ceelen 16 months after resection of a rectal carcinoma. Autopsy disclosed a complex picture of multiple tumour cell emboli in small pulmonary arteries associated with local thrombosis and thrombus-associated vessel wall reaction. This was characterized by movement of medial muscle cells into the thrombus. In addition, affected vessels showed a prominent perivascular tumour-related infiltration by lymphocytes which are identified immunohistochemically as CD3-reactive T-cells.

Key words: Tumour embolism – Thrombendarteriitis – T-lymphocytes – Rectal carcinoma – Pulmonary hypertension

Introduction

Lymphangitis carcinomatosa and paraneoplastic thromboembolism are the most frequent causes of respiratory distress in cancer patients. Alterations of the pulmonary vessels following pulmonary tumour cell embolism with additional local thrombosis, and an organizing reaction in the adjacent vessel wall may also occur and rarely additional perivascular infiltration of lymphocytes can be seen, as first described by Ceelen (1920). He used the term "thrombendarteriitis pulmonalis carcinomatosa". Immunohistological findings obtained from the case of a 65-year-old woman dying in sudden right heart failure 16 months after primary resection of a rectal carcinoma indicate that this peculiar type of arteriitic reactions is characterized by two prominent features: an intense infiltration of the adventitial layer by T-lymphocytes, and migration of smooth muscle cells from the media towards the lumen of the vessel.

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Case report

Clinical data

Sixteen months before death the 65-year-old woman was operated for rectal carcinoma (G_3, T3N2MX). Three weeks prior to death the patient presented with pelvic and left-sided ischial pain. CT revealed a mass of 6×2 cm in front of the sacrum and a suspected slipped disc L5/S1. During hospitalization the thrombocyte count decreased from 241000 10^6/l to 99000 10^6/l. A differential blood cell count was normal. During the last week of life the patient presented with increasing dyspnoea and tachycardia. She died in sudden right heart failure. Clinically, fulminant pulmonary embolism was suspected.

Autopsy findings

Autopsy revealed a local tumour relapse in the pelvis measuring 8×3.5 cm (poorly differentiated adenocarcinoma). The tumour in-

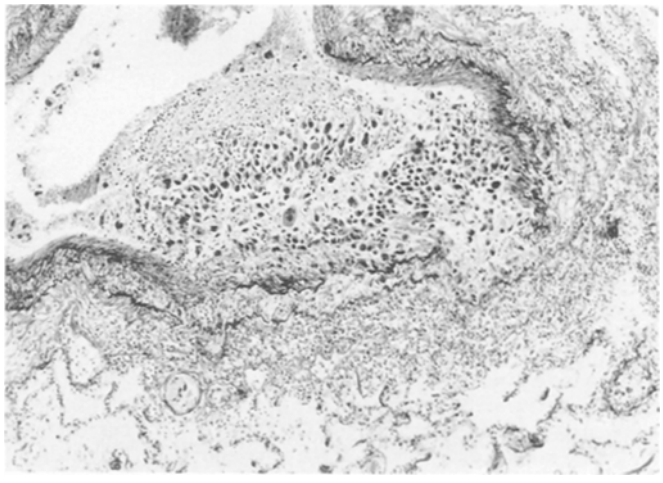

Fig. 1. Pulmonary artery with embolized tumour cells covered by an organising thrombus. Dense perivascular infiltration by lymphocytes. Note predominance of lymphocytic accumulation at the maximal site of destructive vessel wall infiltration. Elastic van Gieson stain, ×180

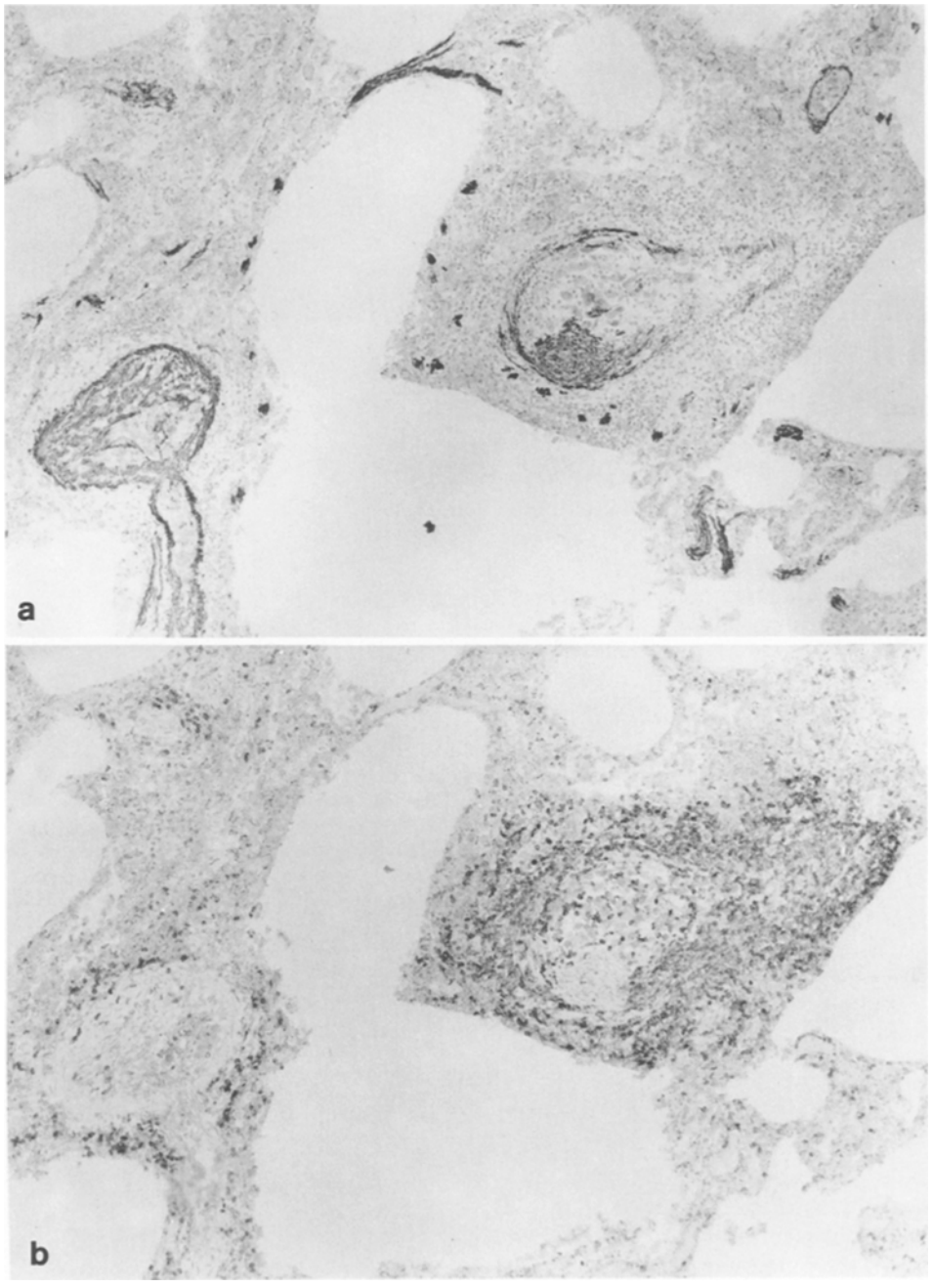

Fig. 2a, b. Small pulmonary arteries occluded by intravascular tumour cells intermingled with thrombotic material. **a** Focal accumulation of alpha-actin-positive smooth muscle cells with rarefication of muscle cells in the neighbouring media. In the lower left corner occlusion of a small artery in a more advanced state of this process. Immunostaining for alpha-smooth muscle actin. **b** Adjacent section to **a** demonstrating the distribution of T-lymphocytes. Immunostaining with antibody UCHL-1, ABC technique, **a**, **b** ×125

filtrated the left ischial nerve, the left internal iliac vein and the sacral spinal column extending into the vertebral canal and infiltrating the cauda equina. On macroscopic examination no lymph node or distant metastases could be found. Fulminant pulmonary embolism was absent. However, several pulmonary arteries measuring 1–2 mm in diameter were occluded by small greyish thrombi. In the right lower lobe two haemorrhagic infarcts measuring up to 2 cm were situated. The adjacent pulmonary artery was occluded by a white thrombus of 5 mm in diameter. Additional findings were cor pulmonale (heart weight 470 g, left to right heart ratio = 1.8) with perivascular fibrosis of the left ventricular myocardium, chronic congestion of liver and spleen, and recent centrilobular liver cell necrosis.

For histological examination paraffin sections were stained with haematoxylin and eosin and elastic van Gieson's stain. Immunohistological investigation was performed using the ABC technique as previously described (Schaefer 1984). Antibodies used were UCHL-1 and CD3 (Dako) for T-lymphocytes, L26 (Dako) for B-lymphocytes, KL1 (Dianova) for cytokeratin, and anti-alpha-smooth muscle actin (Sigma) for smooth muscle cells.

Microscopic investigation revealed a marked alteration of the small pulmonary arteries expecially in the right lung (Fig. 1): more than half of the small arteries were occluded by a thrombotic process. One group of vessels contained large tumour cell emboli. Immunohistologically these cells were stained more or less intensively with a marker for cytokeratin (KL1) (Fig. 3c) and some small arteries were totally occluded. Often tumour cells presented with mitoses. In other vessels the tumour cells were situated intimately adjacent to the intima where concentric as well as eccentric tumour growth could be observed, leading to variable occlusion of the vessel. Very often recent thrombus was present on the surface of the tumour proliferation. In some areas these thrombi were organized by infiltrating alpha-actin-positive smooth muscle cells originating from the adjacent media, from where Indian file-like rows of muscle cells extended into the thrombus (Fig. 2a). As a result, the adjacent media appeared deprived of smooth muscle

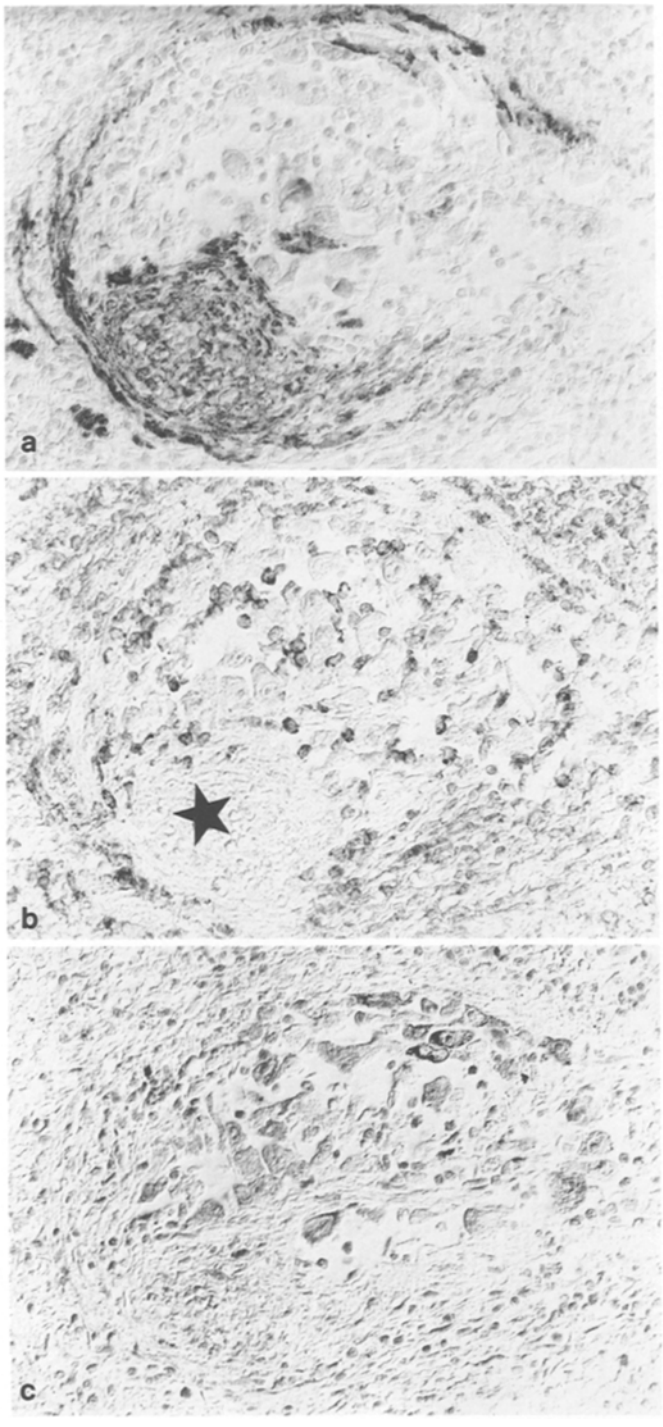

Fig. 3a–c. High power magnification of adjacent sections corresponding to Fig. 2. **a** Embolized tumour cells covered by an organised thrombus. Immunostaining for alpha-smooth actin muscle. **b** Perivascular accumulation of T-lymphocytes with infiltration of intravascular tumour cell embolus. Note absence of lymphocytes in the smooth muscle cell accumulation (*asterisk*). Immunostaining with antibody UCHL-1. **c** Tumour cells intermingled with fine strands of thrombotic material expressing cytokeratin to a varying extent. Immunostaining with KL1, ABC technique. **a–c** × 300

cells and the extent of these defects corresponded to the number of thrombus infiltrating muscle cells (Fig. 3a). Some small arterioles and capillaries contained recent fibrin thrombi as well as old partly recanalized thrombotic lesions. Tumour cells were rare in this type of lesion.

In addition to these alterations most of the affected vessels showed a prominent perivascular infiltration by CD3- and UCHL-1-positive T-lymphocytes (Fig. 2b). L26-reactive B-lymphocytes were virtually absent. These lymphocytic infiltrates were intimately connected to the tumour proliferation, at sites of eccentric intravascular tumour growth, lymphocytes were seen only around the affected part of the vessel wall. Furthermore, dense lymphocytic infiltrates were observed at places where the tumour infiltrated the vessel wall. In some smaller vessels, occluded by intravascular tumour growth, sparse infiltrates of lymphocytes were intermingled within the tumour cells. In contrast, in areas of predominant organization of thrombotic material by smooth muscle cells, no or only a few lymphocytes could be found (Fig. 3b). Veins and lymphatic vessels revealed no pathological changes. Intravascular tumour cells or thrombotic material were not found in any other organ.

Discussion

In 1897 pulmonary tumour embolism was described for the first time (Schmidt 1897) and has been observed in 0.9–3.5% of autopsies in patients with solid neoplasms (Kane et al. 1975; von Herbay et al. 1990 Veinot et al. 1992). Small arteries in the periphery of the lung (Morgan 1949) are mainly affected but cell embolism may rarely occur in capillaries (Soares et al. 1992). In most cases additional lymphangitis carcinomatosa is associated. The most frequent tumours associated with pulmonary tumour cell embolism are carcinomas of the stomach, lung, breast, and less commonly colon. Histologically, many of the primary tumours are mucinous adenocarcinomas (von Herbay et al. 1990).

The extent of tumour cell embolization is not correlated with the number or distribution of distant metastases (Kane et al. 1975). Clinical symptoms occur late in the terminal stage of tumour progression. Sometimes a decrease in thrombocytes or coagulative factors, or a microangiopathic haemolytic anaemia with schistocytes occurring in the peripheral blood may be diagnostic (Klein 1981). However, pulmonary tumour embolization with adjacent thrombosis must be a long-lasting progressive process as is seen by the development of cor pulmonale.

In our case intravascular tumour cells were generally associated with recent thrombi. These associations may be caused by several systemic or local factors; para-neoplastic hypercoagulability can be observed in patients suffering from adenocarcinoma; intravascular tumour cells and damage to the intimal endothelium by infiltrating tumour cells may induce thrombosis by presenting foreign surfaces or causing flow disturbance (Klein 1981).

Obviously these thrombi, and not the tumour cells themselves, produce the vessel wall reaction seen. It is most remarkable that this process is characterized by what appears to be an active movement of medial smooth muscle. This might be induced by the release of platelet derived growth factor which is known to have chemo-attractive activity (Ross 1986). Finger-like infiltration of thrombotic material by smooth muscle cells starts in the media and is associated with a rarefication of muscle cells in the intimately adjacent media, corresponding to the amount of thrombus-infiltrating muscle

cells. So, it is evident that this infiltration by smooth muscle cells is the result of an active movement of medial cells and not of an intimal proliferation as suggested before (von Herbay et al. 1990).

Another very interesting feature is the previously observed perivascular infiltration by lymphocytes (Ceelen 1920). According to our immunohistochemical findings, these lymphocytes are T-cells. Peritumoural infiltration by T-lymphocytes is a well-known phenomenon in carcinoma (von Kleist et al. 1987). However, there is doubt about their presumed anti-tumour specificity. It is worth noting that in our case the lymphocytic infiltration was pronounced, especially in areas of extended tumour growth. In contrast, thrombotic material without tumour cells was not infiltrated by lymphocytes (Fig. 3b). So we conclude that, unlike the thrombus-associated organizing reaction of intima and media, this perivascular T-lymphocytic infiltration is an independent phenomenon caused specifically by tumour growth. One may assume that such a reaction depends on the integrity of the perivascular lymphatic vessels, which was present in our case. Very often in disseminated cancer, these lymphatics are occluded by lymphangitis carcinomatosa. This may be the reason, why there is only one more case in the literature (Greenspan 1934) with this association of intravasal tumour emboli and perivascular lymphocytic infiltration.

Refering to the proposal of Ceelen (1920) this rare complex picture of pulmonary tumour cell embolism with adjacent local thrombosis, thrombus-associated vessel wall reaction and tumour-associated perivascular infiltration of T-lymphocytes should be called thrombendarteriitis pulmonalis carcinomatosa Ceelen.

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