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Case report

Long-term benefit from immune modulation and anti-inflammatory treatment in metastatic mesothelioma

Angus G. Dalgleish [a,*], Emma McLean [b], Nirav Patel [a], Najib Rahman [c]

[a] St George's University Hospital, London, UK
[b] Oncology, Haematology and Cellular Pathology Guy's and St Thomas' NHS Foundation Trust, London, UK
[c] Oxford University Hospitals, Oxford, UK

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ABSTRACT

A 64 year old male heating engineer was investigated for a persistent cough and found to have epithelioid mesothelioma with pleural effusion, lung nodules and increased thoracic lymph nodes. He declined standard of care treatment following his own research and he was enrolled in a named patient programme of IMM-101. He was advised to correct his low vitamin D3 level and to start using anti-inflammatories such as aspirin, bromelain and low dose Naltrexone. At review one year later a CT scan showed no change and he continued on the regimen. Four years after the diagnosis a CT scan showed that there was a modest but definite progression of the left malignant pleural thickening, and a new right-sided effusion, enlargement of several intrathoracic nodes which had been noted on the early scans. The chest wall lump eventually broke down and required local radiotherapy. He then developed abdominal pain and found to have peritoneal disease. Last year he obtained the cannabinoids CBD and THC which slowed down the disease and a CT scan after he had been on this for six months, showed that his disease was fairly stable with marginal progression.

1. Introduction

Mesothelioma is accepted to arise as a direct consequence of asbestos exposure and this often occurs several decades prior to symptoms from the progressing tumour.

Unlike several other cancer types, it does not respond well to chemotherapy and surgery is very rarely curative. In addition to chemotherapy being poorly effective in many cases of mesothelioma, it is also suspected of hastening the progression of the tumour in some circumstances, a feature which is seen with some immunotherapy treatments in a minority of patients.

2. Case presentation

A 64 year old male heating engineer was investigated for a persistent cough and found to have with a pleural effusion, pleural nodules and increased thoracic lymph nodes. Biopsy revealed an epithelioid mesothelioma (Fig. 1). He declined standard of care treatment following his own research into the very low likelihood of cure and the potential side-effects of both the surgery and chemotherapy.

Following informed consent, he was enrolled on a named patient programme of IMM-101 and he was advised to correct his low vitamin D3 level and to start using anti-inflammatories, such as aspirin, bromelain and low dose Naltrexone (LDN). IMM-101 is a suspension of heat-killed whole cell *Mycobacterium obuense,* which enhances the innate immune response and dendritic cell maturation and which has been shown to induce clinical responses in melanoma patients [1] and to increase survival in a randomised study in pancreatic cancer [2]. Naltrexone has been found to be a strong antagonist of TLR9 which is commonly over-expressed in chronic inflammation and several tumour types [3]. IMM-101 was given intradermally in the deltoid area at regular intervals initially every months with no significant toxicities apart from a local reaction at the site of injection.

At review one year later the CT scan showed no change and he continued on the regimen. At a review three years further on, his CT showed slow progression (Fig. 2a). Osteoporosis was also noted and he was started on Zoledronic acid which is of interest as it has innate immune stimulatory properties enhancing gamma delta T-cell activity [4].

Four years after the diagnosis he presented with an enlarging chest wall lesion where the original biopsy had been performed (Fig. 2b). A CT scan showed that there was a modest but definite progression of the left malignant pleural thickening, and a new right-sided effusion with

* Corresponding author. Infection & Immunity Research Centre - St George's, University of London, Cranmer Terrace, London, SW17 0RE, UK.
E-mail address: dalgleis@sgul.ac.uk (A.G. Dalgleish).

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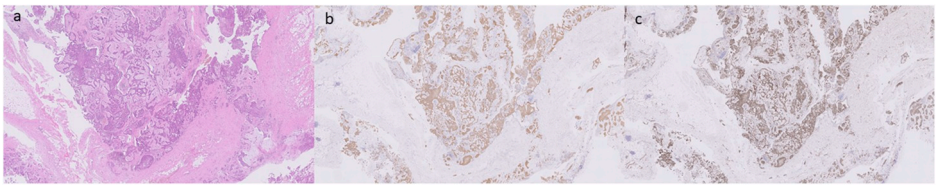

Fig. 1. a) H+E stained section showing an epithelioid mesothelioma: tumour comprised of polygonal epithelial-like cells in a tubulopapillary and acinar growth pattern. No sarcomatoid component seen; b) Strong and diffuse cytoplasmic and nuclear staining for Calretinin indicates mesothelial nature of cells; c) WT1 shows strong nuclear staining, confirming mesothelial cells.

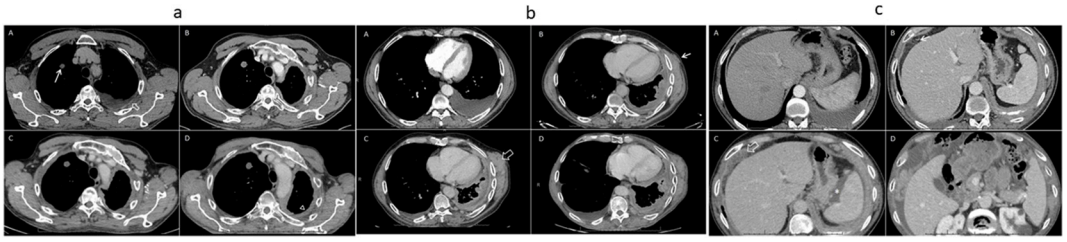

Fig. 2. a) Slow progression of pleural and pulmonary disease. A) Baseline CT demonstrates a small left sided pleural effusion with a subtle nodular pleural disease posteriorly (open arrow). A pulmonary metastasis in the right upper lobe (closed arrow) measures 10mm in maximal diameter at baseline. B, C & D) CT studies at 46 months, 54 months and 65 months respectively post baseline demonstrating a slow interval progression. The pleural disease is circumferential but shows very little change from 46 to 65 months. The right lobe metastasis measures 13mm on all three studies. Fig. 2b) New site of disease developed during treatment in left chest wall at site of previous biopsy. A) No disease seen in left chest wall at baseline CT. B) 31 months CT study demonstrates subtle soft tissue nodule (closed arrow) in left chest wall but patient asymptomatic from this site. C) 50 months CT study demonstrates marked enlargement in the left chest wall mass (open arrow) which is infiltrative within the left serratus anterior muscle. The mass is now symptomatic with new chest wall pain attributed to this disease. D) 65 months CT study demonstrates slight reduction in bulk of left chest wall disease post-radiotherapy. Fig. 2c) New site of disease developed during treatment within the peritoneal cavity. a) No peritoneal disease at baseline. b) New subtle haziness of peritoneum (closed arrow) at 46 months. c) Progression of the peritoneal haziness in the right subphrenic space at 50 months with a small amount perisplenic ascetic fluid (asterix). C) 65 months CT study shows thickened peritoneal metastasis in right subphrenic space with an increase in ascitic fluid.

peritoneal nodularity with enlargement of several intrathoracic nodes which had been noted on the early scans.

The chest wall lump eventually broke down and responded to local radiotherapy. He then developed abdominal pain and was found to have peritoneal disease (Fig. 2c).

Following radiotherapy to his chest wall disease he took no other treatment, apart from a cannabis oil preparation, which he felt improved his symptoms following radiotherapy. CT scans from baseline to 65 months are shown (Fig. 2 a-c).

3. Discussion

The pathogenesis of mesothelioma is a very low grade chronic inflammatory reaction to the asbestos fibres, which over many years leads to collective mutations leading to the mesothelioma.

The importance of chronic inflammation and cancer is well known [5] and the pathogenic association is that chronic inflammation suppresses cell mediated immunity and enhances angiogenic and tumour growth factors. In this environment, random mutations are much more likely to survive and progress than in non-inflamed environments. An example of this is the enhanced development of colon cancer in patients with ulcerative colitis. The chronic inflammation and reduce immune surveillance allow a mutated gene (eg ras) to survive and develop further mutations, aided by growth factors.

On the basis of the known pathogenesis of mesothelioma we proposed our immune-modulatory and anti-inflammatory based programme. IMM-101 enhances the innate immune response as well as inhibiting Th-2 responses. LDN inhibits TLR-9 expression and inflammatory cytokines, such as IL-6. This would reduce the inflammation drive and enhance immunity and hence reduce the inflammatory driven progression of carcinogenesis. This case suggests that this approach should be trialled in similar cases of mesothelioma, particularly in the third of patients with mesothelioma who, like our patient, refuse standard surgery and chemotherapy options.

The patient gave his full written consent for this report and is keen that others can benefit from this treatment.

Declaration of competing interest

Prof Angus G Dalgleish is a member of the scientific advisory board of Immodulon who provided IMM-101 for this patient on a named patient programme.IMM-101-015.

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