Rare presentation of intestinal amyloidosis with acute intestinal pseudo-obstruction and perforation

Gastrointestinal manifestations of amyloidosis include dysmotility and pseudo-obstruction. Here, we report an exceptional case of acute small bowel obstruction followed by perforation in a patient with documented light chain amyloidosis (AL).

A 39 year old Chinese woman had a 10 year history of xerostomia and renal failure requiring dialysis. Her final presentation was precipitated by the acute onset of abdominal pain and vomiting, diagnosed as small bowel obstruction. Laparotomy disclosed jejunal perforation, for which segmental resection was performed. She subsequently died of postoperative complications.

Grossly, the 16 cm long jejunum showed multiple areas of haemorrhagic infarction with one mural perforation site. Histologically, congophilic potassium permanganate resistant green birefringent amyloid was deposited preferentially in vascular channels, particularly in the submucosa, although mesenteric vessels were also involved, and some contained vesicles of organising thrombi. A lesser degree of amyloid deposition was seen only in cases of systemic disease. More commonly, AL results in chronic intermittent bowel obstruction as a result of gut wall deposition of amyloid. The rare cases of gut perforation related to AA have implicated preferential amyloid vascular deposition. In this unique case, the clinical symptoms of acute bowel obstruction complicated by perforation can be explained by an unusual pattern of amyloid deposition in AL, involving both blood vessels and muscularis. Recognition of this rare possibility may facilitate earlier diagnosis in this disease.

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Sensitivity to Quorn mycoprotein (Fusarium venenatum) in a mould allergic patient

A 27 year old female civil servant presented with five episodes of peri-oral, tongue, and neck angio-oedema with wheeze and shortness of breath. One of these episodes occurred a few minutes after eating a Quorn burger. She had a 20 year history of perennial sneezing, rhinorhoea, and itching throat, occurring throughout the day and night, but no cough or wheezing. While on holiday in Mauritius she was asymptomatic. Twelve years previously, she had received six months of weekly injections of alternaria, cladosporium, helminthosporium, and sternymphi as immunotherapy in France. She had no pets, but had noticed mould on her bedroom and bathroom windows.

Skin prick testing and specific IgE results suggested type 1 hypersensitivities to Quorn, Alternaria alternata, Aureobasidium pullulans, cat dander, and grass pollen (table 1). Scrapings from her bathroom and bedroom windows grew heavy growths of Cladosporium sphaeroergum, Rhodotula sp, Aureobasidium pullulans, and fewer numbers of non-sporing mould (Mycology Reference Laboratory, Bristol, UK).

The patient's rhinitis symptoms improved with the regular use of long acting antihistamines, replacing her windows, and controlling humidity at home. She has tried to avoid fungaly contaminated food and has had no further episodes of angio-oedema.

Quorn mycoprotein is produced by Marlow Foods Ltd, from the fungus Fusarium venenatum. Approximately 1/400000 consumers report adverse reactions after eating Quorn. Ten such complainants had negative skin prick tests to an aqueous extract of fresh Quorn. Thirty three Quorn production workers did not have high titres of IgE specific to Quorn, although six known mould allergic subjects did. This study suggested that the risk of sensitisation to Quorn was low, but that patients who were allergic to mould might react adversely to inhaled or ingested mycoprotein. Crossreactivity studies showed that Quorn shared multiple allergenic determinants with Aspergillus fumigatus, Cladosporium herbarum, and Alternaria alternata. Allergen preparations for skin prick testing and specific IgE tests are poorly standardised, and may differ in their potency as much as

Table 1 Allergy testing results

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Skin prick testing</th>
<th>Specific IgE</th>
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<tbody>
<tr>
<td></td>
<td>Wheat (mm)</td>
<td>Flare</td>
</tr>
<tr>
<td>Grass pollen mix</td>
<td>3</td>
<td>++</td>
</tr>
<tr>
<td>Cat dander</td>
<td>4</td>
<td>++</td>
</tr>
<tr>
<td>Dermatophagoides pteronisinus</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Dermatophagoides farinae</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Fresh Quorn mixed with saline</td>
<td>7</td>
<td>++</td>
</tr>
<tr>
<td>Alternaria alternata</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Aspergillus fumigatus</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Cladosporium herbarum</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Aureobasidium pullulans</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

In the skin prick test histamine produced a 6 mm wheal and ++ flare, and saline produced a 0 mm wheal and no flare. Results were those seen 1.5 minutes after using AUK standardised lancets and skin prick test reagents. The specific IgE tests were performed by Sheffield Protein Reference Unit. When Quorn was used as the allergen a small piece of fresh quorn burger was mixed with saline, and a single drop of liquid from the mixture was put on the patient's forearm as with the other skin prick reagents. No specific IgE was detected to two other fusarium species, A. fumigatus and F. oxysporum. Alternaria alternata, Aspergillus fumigatus, and Cladosporium herbarum are reported to cross-react with Quorn. There was a heavy growth of Aureobasidium pullulans in the patient’s home (no tests available to other species isolated).
ND, not done.

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200–3000 fold. The diversity of fungal allergens is a challenge for successful immunotherapy.

A reduction in occupational exposure to fungi may be achieved using helmets with filtered air (which may remove up to 98% of spores), improving ventilation, and controlling humidity. Fungi in dwellings generally rely on the surface, and whether the spores can remain airborne.

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References

Tumour cells produce receptor activator of NF-κB ligand (RANKL) in skeletal metastases

Osteolytic bone destruction is a common complication of tumours that metastasise to bone. Several solid tumours, most notably breast carcinoma, lung carcinoma, and prostate carcinoma, commonly metastasise to bone in patients with advanced disease, where they cause osteolysis and associated pain, hypercalcaemia, and fracture. It is generally accepted that osteoclasts are the only cells capable of resorbing mineralised bone. In osteolytic metastases, it has been shown that tumour cells directly osteolytic bone resorption through a vicious cycle; in particular, tumour cell produced parathyroid hormone related protein (PTH-Pr) facilitates bone resorption and, as a consequence, transforming growth factor β is released from the bone matrix and promotes the progression of bone metastases by further inducing PTH-Pr production by tumour cells. Other tumour cell products, such as macrophage colony stimulating factor, interleukin 6 (IL-6), IL-11, and tumour necrosis factor α, have also been reported to be associated with tumour induced osteolysis.

However, with the identification and characterisation of a direct stimulator of osteoclastogenesis—the receptor activator of NF-κB ligand (RANKL) (also known as ODF, OPGL, and TRANCE)—a possible final common pathway for osteoclast bone destruction has emerged. A variety of osteotropic factors such as 1,25-dihydroxyvitamin D3, prostaglandin E2, parathyroid hormone, IL-6, and IL-11, have been shown to mediate osteoclast differentiation through the upregulation of RANKL expression or the downregulation of osteoprotegerin (OPG) the decoy receptor of RANKL expression in osteoblast/stromal cells. There is also experimental evidence that tumour produced PTH-Pr may stimulate osteoclastic bone resorption by enhancing RANKL expression and reducing OPG expression in the osteoblast. However, whether tumour cells directly produce RANKL, which subsequently mediates osteolysis in metastatic skeletal lesions, has not been determined.

To this end, we have investigated the expression of RANKL in the skeletal lesions of patients with carcinomas that had metastasised to bone. Sixteen cases, including breast carcinoma (four cases), lung carcinoma (six cases), prostate carcinoma (two cases), and follicular thyroid carcinoma (four cases), were collected during surgery of pathological fractures. Histological confirmation of the diagnosis in each case was based on the review of routinely prepared paraffin wax embedded tissue sections in conjunction with knowledge of the clinical and radiological findings. All patients presented with aggressive osteolytic lesions and pathological fracture, and adenocarcinoma was the predominant histological subtype (table 1). The expression of RANKL mRNA and protein was assessed using in situ hybridisation (digoxigenin labelled RANKL antisense riboprobe, 0.5 ng/ml) and immunohistochemistry (mouse antihuman TRANCE monoclonal antibody from R&D, Minneapolis, Minnesota, USA; StreptABComplex/horseradish peroxidase mouse/rabbit system from Dako, Carpinteria, California, USA), respectively, on paraffin wax embedded tissue sections. Typical histological appearances of osteoclast cells in various bone metastatic tumours were revealed by haematoxylin and eosin staining (fig 1, H&E). The neoplastic cells of breast carcinoma, lung carcinoma, prostate carcinoma, and thyroid carcinoma showed strong positive immunoreactivity for RANKL and the primary tumour is predictive of a possible propensity towards skeletal metastasis remains to be seen and could be the focus of future studies.

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Are coroners’ necropsies necessary? A prospective study examining whether a “view and grant” system of death certification could be introduced into England and Wales

The paper by Rutty and colleagues fails to focus upon the key issues raised by the question it seeks to answer. Those issues are: (1) What is the “primary purpose” of coroners’ necropsies? (2) Is the “information available at the time of necropsy” adequate? (3) What is meant by postmortem examination? Does it only mean dissection of the whole body? (4) Under what circumstances should a necropsy be performed without regard to the views of the next of kin?

References


Figure 1  Expression of RANKL mRNA and protein in bone metastatic tumours. Signals are dark blue in colour. RANKL mRNA was present in the neoplastic cells of various metastatic tumours. Positive signals are brown in colour. RANKL protein was present at different intensities in the cytoplasm of the neoplastic cells of various metastatic tumours. All images are at ×200 magnification. In addition, when present in surrounding tissues, osteoblasts and fibroblasts also expressed RANKL mRNA and protein (indicated by arrows). H&E, haematoxylin and eosin staining; ISH, in situ hybridisation; IHC, immunohistochemistry.
in our view, this last issue is the most important and other issues should be dealt with within that context: none of these issues can be dealt with meaningfully without informed public debate. The authors pay lip service only to this question and reach a conclusion ... we consider that necropsies still have an essential role within the coroner’s enquiry” that is self evident but superficial.

The paper seems to be based on a false premise—that the “view and grant” facility could replace necropsies. In this study, the causes of death were predicted in 61–74% of cases; in Glasgow, view and grant is performed on approximately 10% of the deaths with which the necropsy, was not included, because this could have caused bias in the second part of the assessment”. This appears to us a sad inversion of the importance of the issues. The inference may be drawn from the paper that where adequate information was provided, allowing a prediction of cause of death, then “the number of correct predictions made of those where a cause of death had been proffered were as follows: A, 70%; B, 63%; C, 59%”. This appears to us to be the “true error rate”, reducing itself to 30–41%, as opposed to the authors’ preferred 54–61%; we would maintain that one should not include in any determination of “error rate” those cases where a prediction could not be made because of inadequate information: under the view and grant system a necropsy would have been carried out in such cases.

In a paper that attaches so much importance to accuracy of cause of death, it is doubly distressing to find a lack of precision in attributing death to “ischaemic heart disease” without further detail of the pathological basis for ischaemia and in finding “bronchopneumonia” an adequate explanation of death.

We think it unfortunate that this paper does not distinguish between the populations of “natural death” and “unnatural death” or give an indication as to whether any of those deaths that were considered to be natural before necropsy were shown to be unnatural—it is this distinction that appears to us to be the primary purpose of a system of investigation of death in which the wishes of the next of kin are irrelevant.

We welcome the opportunity afforded by the authors to add to the debate regarding the role and future of the coroner system. The authors’ implicit support for more detailed investigation of the circumstances of death before postmortem examination sits well with the “radical option”—foreshadowing a “medical examiner” system—detailed in the Home Office consultation document produced in the first phase of its Review of Death Certification, and with recommendation 11—the feasibility of establishing a new system of death certification involving a medical examiner should be explored”—in recent advice from the chief medical officer.

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References

Androgen receptor expression in ductal carcinoma in situ of the breast: relation to oestrogen and progesterone receptors

We wish to add a reference to the list included in the paper of Selim and colleagues’ concerning androgen receptors in ductal carcinoma in situ (DCIS) of the breast that appeared in the Journal of Clinical Pathology in the first issue of 2002. Although the authors state that androgen receptors in DCIS have not been reported previously, we had studied this and published a paper dealing with our observations, in addition to CAG repeat lengths in the androgen receptor in DCIS.

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References

Authors’ reply
Thank you for this information and the opportunity to reply. Unfortunately, the study of androgen receptor (AR) CAG repeats by Kasami and colleagues is not included in the usual searches and this appears to be the reason for overlooking this reference. In this study, cases of fibroadenoma, ductal carcinoma in situ (DCIS), and invasive mammmary carcinoma were included. Twenty four cases of DCIS were tested for AR CAG repeats and 10 were tested for AR expression immunohistochemically. Two of 10 cases were positive for AR and these two cases were the only cases with apocrine morphology. However, in our study, we found that 19 of 37 cases of DCIS expressed AR. Thirteen of those 19 cases were of non-apocrine morphology. In addition, of the nine morphologically apocrine cases, three lacked AR expression. It seems to be that AR is expressed in some subset of DCIS even within an apocrine morphology, but it is necessarily true that all morphologically apocrine cases of DCIS will express AR. In Kasami and colleagues’ study, none of the cases of invasive mammary carcinoma was tested for AR expression, but other studies have found that a subset of invasive breast carcinomas expresses AR. We feel that a study of AR CAG repeats in benign apocrine metaplasia, which is always immunohistochemically positive for AR, together with and without cases of apocrine and/or non-apocrine in situ and invasive breast carcinoma, would be very valuable in highlighting the importance of CAG repeats and apocrine differentiation.

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