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 frequent diarrhoea and abdominal pain. Her final presentation was precipitated by the acute onset of abdominal pain and vomiting, leading to segmental resection of the bowel. Exploratory 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, conglutic 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 vestiges of organising thrombi. A lesser degree of amyloid deposition was seen within muscularis mucosae and propria, but none was seen in neural plexuses. There was secondary mural acute and chronic ischaemic damage. Ultrastructurally, the amyloid consisted of haphazardly arranged linear nonbranching fibrils of 7-15 nm diameter. The pathological findings were those of AL, preferentially involving vascular channels, with secondary occlusion, and complicating ischaemia with perforation.

This case highlights the clinicopathological differences between the various classes of amyloidosis. Although AL may involve any viscera, the mesenchymal tissues are usually affected.

Gastrointestinal involvement is more common in secondary amyloidosis (AA), especially the mesenteric plexus and vessels, whereas β2 microglobulin amyloid (AH) is usually deposited in periarticular sites. Although AH was a consideration in this case because of the history of dialysis, the ultrastructural features of β2 microglobulin are thick curvilinear fragments of 8-10 nm diameter. Overall, acute bowel infarction and perforation in amyloidosis are rare, and are usually 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.

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 itchy 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 stempylum as immunotherapy in France. She had no pets, but had noticed mould on her bathroom and bedroom 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 sphaerospermum, Rhodotula sp, Aureobasidium pullulans, and fewer numbers of non-sporing mould (Mycology Reference Laboratory, Bristol, UK). The patient's rhinitis symptom improved with the regular use of long acting antihistamines, replacing her windows, and controlling humidity at home. She has tried to avoid fungally 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 1/140 000 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>
</tr>
</thead>
<tbody>
<tr>
<td>Wheat (mm)</td>
<td>Flare</td>
<td>IU/ml Grade</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 pteronysinus</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Dermatophagoides farinace</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>0.4</td>
</tr>
<tr>
<td>Cladosporium herbarum</td>
<td>1</td>
<td>0.6</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 AIL 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, F culmorum and F oxysporum. Alternaria alternata, Aspergillus fumigatus, and Cladosporium herbarum are reported to crossreact 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.
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 reduce up to 98% of spores), improving ventilation, and controlling humidity. Fungi in dwellings generally have no specialised spore liberation mechanisms and largely depend on disturbance. Spore wall structure determines whether allergens are already available on the surface, and whether the spores can remain airborne.

S J Katona, E R Kaminski
Department of Immunology, Level 7, Derriford Hospital, Plymouth, Devon PL6 8HD, UK; katona@doctors.org.uk

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 absorbing mineralised bone. In osteolytic metastases, it has been shown that tumour cells direct osteoclastic bone resorption through a vicious cycle: in particular, tumour cell produced parathyroid hormone related protein (PTH-rP) facilitates bone resorption and, as a consequence, transform growth factor β is released from the bone matrix and promotes the progression of bone metastases by further inducing PTH-rP 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 shown 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 osteoclastic 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-rP 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 anti-human TRANCE monoclonal antibody from R&D, Minneapolis, Minnesota, USA; StreptABCComplex/horseradish peroxidase mouse/rabbit system from Dako, Carpinteria, California, USA), respectively, on paraffin wax embedded tissue sections. Typical histological appearances of neoplastic 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 hybridisations signals with RANKL riboprobe (fig 1, LSH), and also strong positive staining with anti-RANKL antibodies (fig 1, HPC). RANKL mRNA and protein were also present in osteoblasts and fibroblasts in surrounding tissues (fig 1). Table 1 summarises the percentages of tumour cells exhibiting immunoreactivity for RANKL and the intensity of immunostaining in all 16 specimens. In short, we found that both RANKL mRNA and protein were present in more than 90% and in some cases 100% of metastatic tumour cells in lesions of breast, lung, prostate, and thyroid adenocarcinoma. Therefore, we conclude that in osteolytic skeletal secondaries, metastatic tumour cells, regardless of origin, express RANKL, and may directly stimulate osteoclastic bone destruction. In support of our observations, Zhang and colleagues have recently provided evidence that tumour cells of prostate cancer are capable of inducing osteoclastogenesis in vitro, directly through the production of soluble RANKL.

Bone resorption is a necessary priming event for the establishment and propagation of tumour metastasis in bone. Our study has been conducted on the metastatic component of the primary carcinoma in the skeleton, and we did not have access to tissues of the primary site. Indeed, there is a paucity of studies that compare RANKL expression in the primary and metastatic tumours of the same patients. Brown and colleagues reported that RANKL was heterogeneously expressed in 10 of 11 prostate carcinoma specimens, and the proportion of tumour cells expressing RANKL was significantly increased in all bone metastases in comparison with non-osseous metastases or the primary prostate tumour. Whether RANKL expression in the primary tumour is predictive of a possible propensity towards skeletal metastasis remains to be seen and could be the focus of future studies.

Acknowledgements
This study was fully supported by a grant of the Research Grants Council of the Hong Kong SAR (CUHK414200M).

L Huang, Y Y Cheng
Department of Orthopedics and Traumatology, Chinese University of Hong Kong, Shatin, NT, Hong Kong SAR

L T C Chow
Department of Anatomical and Cellular Pathology, Chinese University of Hong Kong

M H Zheng
Department of Orthopaedic Surgery, University of Western Australia

S M Kumta
Department of Orthopedics and Traumatology, Chinese University of Hong Kong; smkumta@cuhk.edu.hk

Table 1 A list of tumour bone metastases and RANKL immunoreactivity

<table>
<thead>
<tr>
<th>Case</th>
<th>Primary site</th>
<th>Diagnosis</th>
<th>RANKL immunoreactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Breast</td>
<td>Adenocarcinoma</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>Breast</td>
<td>Adenocarcinoma</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>Breast</td>
<td>Adenocarcinoma</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>Breast</td>
<td>Adenocarcinoma</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>Lung</td>
<td>Adenocarcinoma</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>Lung</td>
<td>Adenocarcinoma</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>Lung</td>
<td>Adenocarcinoma</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>Lung</td>
<td>Adenocarcinoma</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>Lung</td>
<td>Adenocarcinoma</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>Lung</td>
<td>Adenocarcinoma</td>
<td>95</td>
</tr>
<tr>
<td>11</td>
<td>Prostate</td>
<td>Adenocarcinoma</td>
<td>90</td>
</tr>
<tr>
<td>12</td>
<td>Prostate</td>
<td>Adenocarcinoma</td>
<td>85</td>
</tr>
<tr>
<td>13</td>
<td>Thyroid</td>
<td>Follicular adenocarcinoma</td>
<td>90</td>
</tr>
<tr>
<td>14</td>
<td>Thyroid</td>
<td>Follicular adenocarcinoma</td>
<td>95</td>
</tr>
<tr>
<td>15</td>
<td>Thyroid</td>
<td>Follicular adenocarcinoma</td>
<td>85</td>
</tr>
<tr>
<td>16</td>
<td>Thyroid</td>
<td>Follicular adenocarcinoma</td>
<td>100</td>
</tr>
</tbody>
</table>

www.jclinpath.com

Downloaded from http://jcp.bmj.com/ on June 23, 2017 - Published by group.bmj.com
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.

References

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?
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 Kasami 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.

M Kasami Shizuoka Cancer Center Hospital, Nagazumi, 411–8777, Japan

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.

M Kasami Shizuoka Cancer Center Hospital, Nagazumi, 411–8777, Japan

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 mammary 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 57 cases of DCIS expressed AR. Thirteen of those 19 cases were non-apocrine morphology. In addition, of the nine morphologically apocrine cases, three lacked AR expression. It seems to be that AR is expressed in apocrine ducts even without apocrine morphology, but it is not 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 studies1 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.

A A Selim, G El-Ayat, C A Wells

Department of Histopathology, St Bartholomew’s Hospital, St Bartholomew’s and the Royal School of Medicine and Dentistry, Queen Mary and Westfield College, University of London, West Smithfield, London EC1A 7BE, UK; aaselim@doctors.net.uk
Androgen receptor expression in ductal carcinoma in situ of the breast: relation to oestrogen and progesterone receptors
M Kasami and D L Page

J Clin Pathol 2002 55: 879
doi: 10.1136/jcp.55.11.879

Updated information and services can be found at:
http://jcp.bmj.com/content/55/11/879

These include:

References
This article cites 4 articles, 2 of which you can access for free at:
http://jcp.bmj.com/content/55/11/879#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/