Xanthoma disseminatum with respiratory tract involvement and fatal outcome

Christopher W H Davies, Pauline Marren, Mark C Juniper, Winifred Gray, Fenella Wojnorowska, Malcolm K Benson

Abstract
Xanthoma disseminatum (XD) is a rare mucocutaneous xanthomatosis classified as a benign form of non-Langerhans’ cell histiocytosis. The case history is presented of a 61 year old woman with XD who developed dyspnoea and spirometric features of airflow obstruction. Bronchoscopy and computed tomography confirmed involvement of the large and medium sized bronchi and she subsequently died from acute respiratory failure. The post-mortem findings and the importance of respiratory tract disease in this unusual condition are discussed.

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Keywords: xanthoma disseminatum; respiratory tract

Xanthoma disseminatum (XD) is a rare, benign mucocutaneous xanthomatosis caused by the proliferation of non-X histiocytic cells. It is characterised by widespread cutaneous xanthomas and may affect the mucous membranes of the mouth and upper respiratory tract, but involvement of the lower respiratory tract is extremely uncommon. We present a case of XD affecting the skin, upper airways, and also the lower respiratory tract leading to death by respiratory failure. The importance of respiratory tract involvement in XD is discussed.

Case report
In December 1993 a 61 year old woman presented with a two month history of asymptomatic “warty” lesions on her vulva but also involving the axillae, submammary areas and, to a lesser extent, the upper limbs. The lesions were variable in size, appearing as smooth yellow papules some of which were confluent, and one vulval lesion was becoming large and uncomfortable. The patient’s full blood count, erythrocyte sedimentation rate, C-reactive protein, urea, electrolytes, liver function tests, thyroid function, lipid profile, glucose tolerance test, serum immunoglobulins, and serum and urine electrophoresis were all normal. Biopsy specimens from the vulva and skin showed different stages of the time course of this entity with vacuolated histiocytic cells interspersed with mixed inflammatory infiltrate and giant cells (fig 1A). There was a predominance of fibrotic changes with predominantly spindle shaped histiocytes in the larger nodular lesions. Immunocytochemical tests were negative for markers of histiocytosis-X (S100 protein, LN3 and peanut agglutination) and positive for factor XIIIa, HAM 56, and KP1. There were no cells containing Birbeck granules at electron microscopy and the cells showed an irregular scalloped border with a centrally placed nucleus. In view of the clinicopathological presentation and immunocytochemical markers the diagnosis of xanthoma disseminatum was confirmed. She was commenced on topical clobetasol propionate 0.05% over the following few months she developed lesions elsewhere on the trunk and buttocks with little response to the topical steroids.

In February 1995 she developed dyspnoea, wheeze, and a weak voice. Examination at that time revealed a fixed wheeze in the left lung and slight hoarseness of the voice. Spirometric tests revealed obstructive airflow with a forced expiratory volume in one second (FEV1) of 1.0 litre (40% predicted) and forced vital capacity (FVC) of 2.5 litres (85% predicted). The chest radiograph was unremarkable. Bronchoscopic examination showed bilateral vocal cord oedema and a nodule at the anterior commissure. Throughout the trachea and main airways there were numerous flat pale white lesions and biopsy specimens showed a mucosal infiltrate of histiocytic cells with a foamy cytoplasm. There was no evidence of granuloma formation and Ziel-Nielsen stain failed to reveal acid fast bacilli. Blood investigations including serum angiotensin converting enzyme (ACE) were normal. She was commenced on oral prednisolone 10 mg daily and after six months of monitored treatment there had been no subjective or objective evidence of improvement in the chest. The prednisolone was reduced to 5 mg daily without deterioration in symptoms.

In 1996 she was reviewed and still complained of a weak voice and dyspnoea. During the interval she had continued to develop further cutaneous lesions consistent with XD. Chest examination was normal. Pulmonary function tests were unchanged and confirmed airflow obstruction: FEV1 1.0 litre (40% predicted) and FVC 2.6 litres (87% predicted) with normal gas transfer. Flow volume loops excluded fixed upper airway obstruction. Computed tomographic (CT) scanning of the thorax showed significant thickening of the trachea and large airways, and minor bronchial wall thickening throughout the lungs. There was no evidence of interstitial lung disease. Blood investigations were again normal. She was given a trial of inhaled beclomethasone which had no beneficial effect and was discontinued after two months.
The patient was reassessed in 1997 because of worsening dyspnoea. Chest examination was again unremarkable and oxygen saturation was 95%. FEV1 had fallen slightly to 0.8 litres. A repeat bronchoscopic examination showed small submucosal nodules in the trachea and main airways, but biopsy specimens were non-diagnostic.

Forty eight hours later she became increasingly unwell and suffered a respiratory arrest at home. Resuscitation was unsuccessful and necropsy examination confirmed numerous submucosal nodules in the trachea and all the bronchi (fig 1B). Nodules were also present on the visceral pleura, epicardium, and the lower third of the oesophagus. Histologically all of these tissues showed infiltration of foamy macrophages and histiocytic proliferation with lipid storing cells and immunocytochemical examination confirmed that they were also non-X histiocytic cells (fig 1C). There was no cytological atypia or evidence of neoplastic transformation in any of the sites; these have been compared with histological examination of the skin and confirm the appearances of XD. The cause of death was stated as respiratory failure and bronchospasm secondary to XD.

Discussion

Xanthoma disseminatum is one of several heterogeneous conditions known collectively as the primary histiocytic dermatoses or cutaneous syndromes of non-X histiocytoses, so called to differentiate them from the more recognised condition histiocytosis-X (HX). The condition is caused by a proliferation of non-X histiocytic cells, probably from a macrophage/monocyte origin, and was probably first described in 1867 by von Grafe and subsequently as a distinct entity by Montgomery and Osterberg in 1938. Only about 100 cases of XD have been reported in the world literature; the condition appears to affect predominantly male children and young adults but has been described in both sexes and in all age groups.

As XD and HX share clinical and pathological features, difficulties may arise in diagnosis but immunocytochemical and ultrastructural differences have recently been recognised.

Electron microscopy shows Birbeck (Langerhans') granules in HX which are absent in XD, while more phagosomes are seen in XD and other non-X histiocytoses compared with HX.

Immunocytochemistry has shown differences between the proliferating Langerhans' cells in HX which label positively for S-100, LN3, and peanut agglutination in contrast to cells of macrophage/monocyte origin in XD (and other non-X histiocytoses) which are strongly positive for factor XIIIa, KiM6, and KP1 markers.

Typically XD affects the flexural areas and skin lesions may regress spontaneously after several years. More commonly a persistent mucocutaneous form occurs and treatment with steroids, immunosuppressive agents, and radiotherapy is usually unsuccessful despite the successful use of agents such as etoposide, the vinca alkaloids, and methylprednisolone in Langerhans' cell histiocytosis.

Selective cutaneous lesions in XD may be ablated by dermabrasion or electrodesication. Diabetes insipidus is a common systemic manifestation of the disease but may be mild and transient and involvement of mucous membranes may be observed in 30–50% of cases, typically affecting most frequently (in order) the larynx, pharynx, mouth, trachea, epiglottis, and tongue.

When the pharynx and upper airways are involved symptoms of dyspnoea and dysphagia may occur and endoscopic examination may reveal plaques covering the mucosal surfaces. These can cause life threatening obstruction and asphyxiation requiring tracheostomy and has been reported in a total of eight patients. This is the most recognised cause of morbidity in XD, but tracheostomy...
may successfully relieve obstruction to the larynx with patients continuing in good health at subsequent follow up.

In our patient necroscopy showed no evidence that upper airway obstruction was responsible for asphyxiation but that death was caused by bronchospasm secondary to extensive involvement of the medium and small sized bronchi leading to respiratory failure. This complication has not been described since 1925 when Turner et al.1 reported the death of a 22 year old girl with XD who also died from respiratory failure secondary to airway infarction including the bronchi. Although infarction of the bronchi has been reported at necropsy in one other case of XD,2 it was not the cause of death as seen in our patient.

Xanthoma disseminatum is a rare mucocutaneous xanthomatosis considered to be benign and self-limiting and unresponsive to various modes of treatment. Involvement of the larynx may, however, lead to life threatening complications necessitating tracheostomy with a satisfactory long term prognosis but, when the lower respiratory tract is affected as in this case, the prognosis is poor leading to respiratory failure and death.

Letters, Notice

Table 1 Distribution of the cumulative exposure (mg/m² • years)

<table>
<thead>
<tr>
<th></th>
<th>Stone &amp; quarrying</th>
<th>Ceramics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 133)</td>
<td>(n = 231)</td>
</tr>
<tr>
<td>Cases</td>
<td>Controls</td>
<td>Cases</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.12</td>
<td>0.15</td>
</tr>
<tr>
<td>10%</td>
<td>0.85</td>
<td>0.54</td>
</tr>
<tr>
<td>25%</td>
<td>1.76</td>
<td>1.34</td>
</tr>
<tr>
<td>50%</td>
<td>3.24</td>
<td>2.70</td>
</tr>
<tr>
<td>75%</td>
<td>8.12</td>
<td>4.19</td>
</tr>
<tr>
<td>90%</td>
<td>16.13</td>
<td>6.17</td>
</tr>
<tr>
<td>Maximum</td>
<td>25.92</td>
<td>22.32</td>
</tr>
</tbody>
</table>

For a man of 20 years and height 180 cm (for whom, according to table 2, the predicted FEV1 value is 4.696), the 5th percentile of FEV1 is computed as follows: FEV1 = 4.696 e^{−0.143 − 0.00158 * 20} = 3.944.

Re-estimated equations for 5th percentiles of lung function variables

In 1996 we published reference equations for the 5th percentiles of lung function parameters (FEV1, FVC, FEV1/FVC, FEF25−75, FEF50) as a function of age and height. These reference values were derived from the subsample of the Swiss SAPALDIA study population consisting of never smokers without respiratory symptoms (1267 men and 1890 women aged between 18 and 60 years). In the meantime our German colleagues have applied extrapolations of the 5th percentile curves to men aged between 60 and 70 years and have found that for some of the lung function parameters—for example, FEV1—the 5th percentiles appeared to get too close to the mean at age 70 (fig 1).

A new method of estimating percentile curves provides slightly different estimates of the 5th percentile with more plausible extrapolations. This method uses weighted L_2 regression. Thus, instead of minimising the sum of squared residuals, a weighted sum of the absolute values of the residuals is minimised. For instance, in order to obtain an estimate of the 5th percentile curve, the weight assigned to terms stemming from negative residuals must be 19 times larger than the weight assigned to terms whose underlying residual is positive. (As in our original approach, we used the logarithms of individual ratios between observed and predicted lung function values (LF) as the basis for estimating the 5th percentile curves.) These residuals were regressed against age using weighted L_2 regression as described above. If y = u + β age denotes the estimated regression line for the 5th percentile of LF given age. To test whether a linear age term was necessary, the residuals were regressed against age and a quadratic term was added if the resulting regression coefficient was significantly different from zero. The new method then minimises the weighted sum of squared residuals.

The new method of estimating percentile curves differs from the original approach in two respects. First, the logarithms of individual ratios between observed and predicted lung function values were used as the basis for estimating the 5th percentile curves. In the original approach, we used the absolute values of the residuals as the basis for estimating the 5th percentile curves. Second, the new method uses weighted L_2 regression. Thus, instead of minimising the sum of squared residuals, a weighted sum of the absolute values of the residuals is minimised. For instance, in order to obtain an estimate of the 5th percentile curve, the weight assigned to terms stemming from negative residuals must be 19 times larger than the weight assigned to terms whose underlying residual is positive. (As in our original approach, we used the logarithms of individual ratios between observed and predicted lung function values (LF) as the basis for estimating the 5th percentile curves.) These residuals were regressed against age using weighted L_2 regression as described above. If y = u + β age denotes the estimated regression line for the 5th percentile of LF given age. To test whether a linear age term was necessary, the residuals were regressed against age and a quadratic term was added if the resulting regression coefficient was significantly different from zero. The new method then minimises the weighted sum of squared residuals.
For a man of 20 years and 180 cm the predicted value of FEV1 is computed as follows:

FEV1 = \( e^{(-9.280 + 1.9095 \ln(180) + 0.0795 \times 20 - 0.001698 \times 400)} = 4.696 \)

For a woman of 20 years and 180 cm the predicted value of FEV1 is computed as follows:

FEV1 = \( e^{(-8.217 + 1.8475 \ln(H) + 0.0035A - 0.000130A^2)} \) 

The quadratic age term did not reach statistical significance for any of the lung function parameters considered. However, this does not prove the validity of these extrapolations. Only empirical data on lung function from a sample of healthy never smoking subjects older than 60 years could provide truly reliable estimates of lung function parameters at this age. The original and revised estimates of the 5th percentiles of FEV1 for men and women are shown in figs 1 and 2.

### Table 2 Prediction equations for the means of lung function variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (l)</td>
<td>( \text{FVC} = \exp(-10.321 + 2.1685 \ln(H) + 0.0655A - 0.001325A^2) ) (A≤25)</td>
</tr>
<tr>
<td>FEV1 (l)</td>
<td>( \text{FEV1} = \exp(-9.540 + 2.1685 \ln(H) + 0.0030A - 0.000075A^2) ) (A≤25)</td>
</tr>
<tr>
<td>PEF (l/s)</td>
<td>( \text{PEF} = \exp(-8.240 + 1.9095 \ln(H) - 0.0037A - 0.000033A^2) ) (A&gt;25)</td>
</tr>
<tr>
<td>MEF25 (l/s)</td>
<td>( \text{MEF25} = \exp(-4.757 + 1.1220 \ln(H) - 0.0035A - 0.000033A^2) )</td>
</tr>
<tr>
<td>MEF50 (l/s)</td>
<td>( \text{MEF50} = \exp(-2.332 + 0.7376 \ln(H) + 0.0045A - 0.000166A^2) )</td>
</tr>
<tr>
<td>MEF75 (l/s)</td>
<td>( \text{MEF75} = \exp(-4.048 + 1.1453 \ln(H) + 0.0020A - 0.000068A^2) )</td>
</tr>
<tr>
<td>MEF25–75 (l/s)</td>
<td>( \text{MEF25–75} = \exp(-3.205 + 0.9457 \ln(H) - 0.0025A - 0.000137A^2) )</td>
</tr>
<tr>
<td>PEF (l/s)</td>
<td>( \text{PEF} = \exp(-6.189 + 1.2965 \ln(H) + 0.0042A - 0.000082A^2) )</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>( \text{FEV1/FVC} = \exp(1.526 - 0.3144\ln(H) - 0.0033A) )</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>( \text{FVC} = \exp(-10.321 + 2.1685 \ln(H) + 0.0655A - 0.001325A^2) ) (A≤25)</td>
</tr>
<tr>
<td>FEV1 (l)</td>
<td>( \text{FEV1} = \exp(-9.280 + 1.9095 \ln(H) + 0.0795A - 0.001698A^2) ) (A≤25)</td>
</tr>
<tr>
<td>Men</td>
<td>( \text{FVC} = \exp(-9.457 + 2.0966 \ln(H) + 0.0091A - 0.000152A^2) ) (A&gt;25)</td>
</tr>
<tr>
<td>Women</td>
<td>( \text{FVC} = \exp(-9.457 + 2.0966 \ln(H) + 0.0091A - 0.000152A^2) ) (A&gt;25)</td>
</tr>
<tr>
<td>Men</td>
<td>( \text{FEV1} = \exp(-9.540 + 2.1685 \ln(H) + 0.0030A - 0.000075A^2) ) (A&gt;25)</td>
</tr>
<tr>
<td>Women</td>
<td>( \text{FEV1} = \exp(-9.280 + 1.9095 \ln(H) + 0.0795A - 0.001698A^2) ) (A&gt;25)</td>
</tr>
</tbody>
</table>

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**Figure 2** Mean and 5th percentile of FEV1 in women of height 1.65 m as a function of age (based on cross sectional lung function data from healthy never smoking women aged 18–60 years). Original and revised estimates of the 5th percentiles are shown.

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The quadratic age term did not reach statistical significance for any of the lung function parameters considered, thus suggesting that the new model was sufficient throughout. In an analogous way we could verify that the 5th percentile of FEV1 did not significantly depend on the height of the person. Our new estimates of the parameters α and β are shown in table 1. For the sake of completeness we reproduce in table 2 the equations for the means of lung function parameters previously published.1

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**NOTICE**

A course on Pulmonary Pathology designed to provide histopathologists and cytopathologists with an opportunity to study diagnostic lung pathology in a comprehensive manner will be held at the Imperial College School of Medicine, National Heart & Lung Institute, London on 20–23 June 2000. Further details and application forms are available from Professor B Corrin, Brompton Hospital, London SW3 6NP. Fax: +44 20 7351 8293. Email: b.corrin@ic.ac.uk.
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