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.

(Thorax 2000;55:170–172)

Keywords: xanthoma disseminatum; respiratory tract

Xanthoma disseminatum (XD) is a rare, benign mucocutaneous xanthomatosis caused by the proliferation of non-X histiocytes. 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 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 cutaneous lesions consistent with XD. Chest examination was normal. Pulmonary function tests were unchanged and confirmed airflow obstruction: FEV\(_1\) 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 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 (FEV\(_1\)) 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: FEV\(_1\) of 1.0 litre (40% predicted) and FVC 2.6 litres (87% predicted) with normal gas transfer. Flow volume loops 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 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 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 (FEV\(_1\)) 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: FEV\(_1\) of 1.0 litre (40% predicted) and FVC 2.6 litres (87% predicted) with normal gas transfer. Flow volume loops 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 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: FEV\(_1\) of 1.0 litre (40% predicted) and FVC 2.6 litres (87% predicted) with normal gas transfer. Flow volume loops 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 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.
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 necroscopic examination confirmed numerous submucosal nodules in the epiglottis, trachea, and all the bronchi (fig 1B). Nodules were also present on the visceral pleura, the 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...
Silica dust and lung cancer

We appreciate the recent contribution of Ulm et al2 to the controversial question as to whether occupational exposure to crystalline silica, a classified carcinogen, increases the risk of lung cancer irrespective of silicosis. There are, however, some serious conceptual and methodological questions regarding the design, conduct, and analysis of the study which may affect the conclusions.

If silicosis is a surrogate for the internal dose or on the causal pathway between silica exposure and lung cancer, this question might only be addressed with detailed individual exposure information and classification of the silicosis grade in a population of silicotic and non-silicotic subjects.

The authors presented the pooled data from two matched case-control studies among non-silicotic subjects in two German industries. The study populations were not clearly defined with respect to the region. Cohorts for the recruitment of cases and controls as suggested by the authors cannot be reconstructed. Given the lack of a nationwide cancer registry in Germany, complete case ascertainment is questionable. In particular, the selection of potential cases from the workforce due to health problems poses a threat to internal validity.

Recruitment of controls and exposure levels varied between the two industries. Selection of more highly exposed or silicotic control subjects, in particular in the stone and quarrying industry, cannot be ruled out. We think that more detailed information on the data and results from the two industries, which have been presented in a previous German report of this study,7 is crucial for the interpretation of the results. Discrepant results between the two industries and between different publications of this study ought to be discussed.

The authors made a great effort to reconstruct the exposure to silica dust. However, the quality and completeness of the exposure data remain questionable because the exposure assessment was retrospective and no figures on missing dust measurements were presented.

The baseline risks of the cases and controls were high (cumulative exposure >0.12 mg/m³ * years) which may render the detection of an additional risk of lung cancer in this study population difficult. Could the restriction to highly exposed individuals explain the low relative risks of lung cancer in this study?

In the previous report of this case-control study, which included subjects with silicosis, the risk estimates of lung cancer for the three exposure indices were relatively low and not significant. Why do the authors expect the risks to be higher after excluding those with silicosis?

The authors presented only adjusted odds ratios. We appreciate the control of confounding by other occupational exposures. However, if the duration of exposure is a surrogate for the investigated exposure, an additional risk might not be observed after adjustment for duration of exposure.

The authors matched subjects on smoking status yet, in the previous report, an index of smoking intensity and duration was a significant risk factor for lung cancer and the smoking adjusted risk estimates were slightly higher than the risk estimates reported in this paper.8 Why did the authors not adjust for smoking as in the previous report?

In general, details on excluded and deceased subjects, coding of variables, missing data, and statistical methods presented in this paper were not easily verifiable. In the discussion the authors concluded that the study showed no association between exposure to crystalline silica and lung cancer which might either be a true finding or be attributed to a lack of statistical power. Like previous studies of non-silicotic subjects9 this study lacked the power to detect risks of 1.4 or less. In addition, all potential sources of bias (non-differential misclassification of the exposure, selection bias, and healthy worker effect) lead to an underestimation of the risk estimates. We would therefore suggest that the results are interpreted with caution. It remains unclear whether silicosis is on the causal pathway between exposure to silica and lung cancer.

X BAUR
U LATZA
BGFA, Institute at the Bular-Universität Bochum, Buitele-de-la-Camp-Platz 1, D 44789 Bochum, Germany

K-H JÖCKEL
Institute for Medical Informatics, Biometry and Epidemiology, University Clinics of Essen, D-45122 Essen, Germany


AUTHORS’ REPLY We appreciate the comments of Baur and colleagues on our paper.1 In Germany it is difficult to perform epidemiological studies due to the lack of registries and some regulations, therefore in case-

LETTERS TO THE EDITOR
control studies complete case ascertainment can never be guaranteed. We checked all the sources available to identify all cases with lung cancer in the selected area of Germany. The main question, however, is whether the group of cases enrolled is selected and not a random sample. There are no indications for that bias with respect to the exposure.

The selection of controls can be a problem in case-control studies, especially if there is no file of all possible controls available, which is the situation in the stone and quarrying industry. As already mentioned in the paper, for this type of industry the so-called accident file has been used. The possibility of a selection bias cannot be ruled out. However, most of the accidents are based on carelessness such as stumbling. Whether those accidents are related to any exposure levels is highly speculative.

Due to lack of space in the paper the data reported had to be condensed. In table 1 the distribution of the cumulative exposure for both industries is given separately. There is a difference between both industries with respect to higher exposures. The level of exposure in both industries is comparable to the other studies and not exceptionally high as stated by the authors of the letter. In the monograph by IARC the geometric mean for the ceramic industry varied between 0.01 and 0.44 mg/m³ with a range of 0.01–1.14 mg/m³. The level in the quarrying industry is higher with a mean value of 0.03–2.1 mg/m³ and peak values over 100 mg/m³.

Assessment of the exposure in occupational epidemiology is mostly based on retrospective estimates and not on measurements. Within this study great effort has been made to quantify the exposure. If measurements were available these have been taken into account.

If the smoking habits are included in the model the fit improves considerably. In the analysis of the average exposure the likelihood ratio value is 386.62 with smoking and 345.72 without. However, the estimates of the odds ratio for the average exposure without silicosis were available these have been taken into account for silica dust in order to prevent silicosis and therefore to exclude, or at least minimise, the associated risk of lung cancer.

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, FEV₉, PEF, FEF₂₅₋₇₅, FEV₁/FVC) 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_r 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. ² 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_r regression as described above. If y = µ + βx denotes the estimated regression line for the 5th percentile of LF given age x. To test whether a linear age term was sufficient to describe the age dependency of the 5th percentile of r we

<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>FEV₁, new</th>
<th>FEV₁, old</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>1.69</td>
<td>1.70</td>
</tr>
<tr>
<td>160</td>
<td>1.71</td>
<td>1.73</td>
</tr>
<tr>
<td>170</td>
<td>1.72</td>
<td>1.74</td>
</tr>
<tr>
<td>180</td>
<td>1.73</td>
<td>1.75</td>
</tr>
</tbody>
</table>

Table 1 Parameters of the multiplicative factor F_{5 \text{th}} = \exp(\alpha + \beta \text{age}) by which the predicted value from table 2 must be multiplied in order to get the 5th percentile value for the given age and height

For a 20 year old 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^{0.140 + \text{height} \times 0.00112} = 5.154.
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></td>
</tr>
<tr>
<td>FEV₁ (l)</td>
<td>exp (−10.321 + 2.1685 ln (H) + 0.0655A - 0.001325A²) (A≤25)</td>
</tr>
<tr>
<td>FEF (l/s)</td>
<td>exp (−9.540 + 2.1685 ln (H) - 0.0030A - 0.000075A²) (A≥25)</td>
</tr>
<tr>
<td>MEF₂₅ (l/s)</td>
<td>exp (−4.757 + 1.1220 ln (H) - 0.0035A - 0.000033A²) (A≥25)</td>
</tr>
<tr>
<td>MEF₅₀ (l/s)</td>
<td>exp (−8.465 + 1.0489 ln (H) - 0.0020A - 0.000020A²)</td>
</tr>
<tr>
<td>MEF₇₅ (l/s)</td>
<td>exp (−6.790 + 0.9869 ln (H) - 0.0011A - 0.000011A²)</td>
</tr>
<tr>
<td>MEF₂₅–₇₅ (l/s)</td>
<td>exp (−7.740 + 0.9457 ln (H) - 0.0015A - 0.000013A²)</td>
</tr>
<tr>
<td>PEF (l/s)</td>
<td>exp (−5.790 + 1.2965 ln (H) - 0.0042A - 0.000082A²)</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>exp (−1.526 − 0.3144 ln (H) - 0.0027A)</td>
</tr>
<tr>
<td>MEF₂₅ (l/s)</td>
<td>exp (−4.474 + 1.1258 ln (H) - 0.0012A - 0.000011A²)</td>
</tr>
<tr>
<td>MEF₅₀ (l/s)</td>
<td>exp (−2.510 + 0.8156 ln (H) + 0.0012A - 0.000119A²)</td>
</tr>
<tr>
<td>MEF₇₅ (l/s)</td>
<td>exp (−4.440 + 0.9869 ln (H) + 0.0011A - 0.000011A²)</td>
</tr>
<tr>
<td>MEF₂₅–₇₅ (l/s)</td>
<td>exp (−3.205 + 0.9457 ln (H) − 0.0025A - 0.000137A²)</td>
</tr>
<tr>
<td>PEF (l/s)</td>
<td>exp (−6.189 + 1.2965 ln (H) + 0.1379A - 0.002731A²)</td>
</tr>
<tr>
<td>FEV₁ (l)</td>
<td>exp (−9.280 + 1.9095 ln (H) + 0.0795A - 0.001698A²)</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>exp (−10.321 + 2.1685 ln (H) + 0.0655A - 0.001325A²)</td>
</tr>
</tbody>
</table>

A = age (years); H = height (cm); exp(x) = e^x

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

\[ FEV₁ = e^{(−9.280 + 1.9095 \times \ln(180) + 0.0795 \times 20 − 0.001698 \times 400)} = e^{1.547} = 4.696. \]

In contrast to our original estimates of the 5th percentile equations, those derived with the new method appear to provide plausible-extrapolations beyond the age of 60 years for all 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.

### Course on Pulmonary Pathology

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.
Xanthoma disseminatum with respiratory tract involvement and fatal outcome

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

Thorax 2000 55: 170-172
doi: 10.1136/thorax.55.2.170

Updated information and services can be found at:
http://thorax.bmj.com/content/55/2/170

These include:

References
This article cites 10 articles, 0 of which you can access for free at:
http://thorax.bmj.com/content/55/2/170#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.

Topic Collections
Articles on similar topics can be found in the following collections
Cardiothoracic surgery (676)

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/