Computed tomography abnormalities antedating mesothelioma diagnosis: a perspective on the natural history

To the Editor:

Malignant pleural mesothelioma (MPM) is an aggressive and fatal disease that typically presents with breathlessness, chest pain or both [1]. It is usually a unilateral disease but 3% of patients have malignant disease bilaterally at presentation [2]. The latency period between exposure to asbestos and MPM development is 20–40 years.

Computed tomography (CT) is the best imaging modality to assess for malignant pleural involvement [2]. Involvement of inter-lobar fissures and circumferential pleural involvement with hemithorax contraction suggest MPM [3, 4], but neither of these signs is specific enough to rule out other causes of pleural malignancy. In addition, tumour thickness measured by CT is the standard method to measure MPM response to therapy, although CT tumour volumetry is another method under investigation [5]. Patients with MPM frequently, but not invariably, have CT evidence of other asbestos-related pleural disease. These include plaques, diffuse thickening and effusion. The frequency of these abnormalities and their distribution in relation to MPM is not well characterised. Additionally, CT has a low negative predictive value in asbestos-exposed patients who present with a bland-looking effusion; often a pleural biopsy is needed to differentiate MPM from benign asbestos-related effusion [6]. We aimed to study chest CT findings in scans conducted before a diagnosis of MPM was made to learn more about the evolution of MPM, and the natural history of early radiological features, with a view to identifying radiological change which was potentially "at risk" of later progression to mesothelioma.

In a retrospective study of the local database of mesothelioma patients diagnosed at Oxford University Hospitals (Oxford, UK) between 2009 and 2017, patients' electronic records were screened for chest CT scans before the diagnostic CT that suggested a diagnosis of mesothelioma. Patients' clinic letters were examined to extract details about asbestos exposure, concurrent malignancy and mesothelioma tissue type. The following radiological details were sought: the indication for each scan and the presence of pleural abnormalities (namely, effusion, thickening and plaques). CT scans were grouped into three time periods: within 1 year prior to the diagnostic CT scan (period A); 1–3 years before diagnosis (period B); and >3 years before diagnosis (period C).

Out of 190 patients in the database, 47 had CT scans antedating the diagnosis of MPM. 11 (23.4%) patients were diagnosed on a clinico-radiological basis either due to repeated negative biopsies or frailty precluding any invasive diagnostic testing. 36 (76.6%) patients were histologically confirmed (26 epithelioid, six biphasic, three sarcomatoid and one desmoplastic pathology). The median (interquartile range) age of patients was 80 (69–84) years, and 11 patients (23.4%) had history of previous unrelated malignancy. 39 (82.9%) patients were males, and previous asbestos exposure was documented in 32 (68%) patients. The mean (95% CI) time from diagnosis to death in this cohort was 17.8 (11–24) months. For the epithelioid histology, mean survival was 22.8 (14–31) months, for biphasic, it was 11.2 (4.8–17.5) months and for clinical diagnosis it was 4.4 (1.9–7.6) months.

76 pre-diagnosis CT scans were available for analysis. The mean time between a CT scan and diagnosis was 18 months (range 12–36 months; minimum 5 months, maximum 109 months). 21 scans (for 18 patients)

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Radiological evolution of MPM is difficult to infer. Previous pleural effusion or thickening warrants careful follow-up. Some patients don't exhibit abnormalities a few months prior to diagnosis while others carry pleural abnormalities for several years. http://ow.ly/uTGO30mJ8D2

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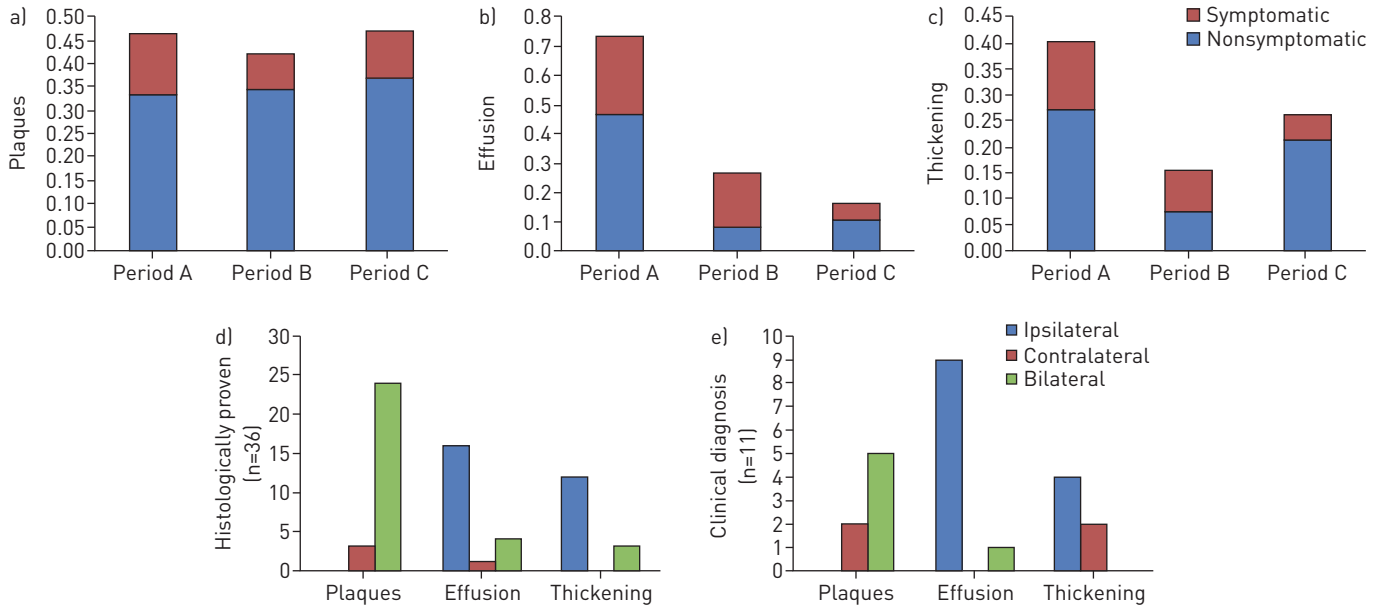

FIGURE 1 a–c) Proportion of different pleural abnormalities in pre-diagnosis computed tomography (CT) scans in the three time periods for histologically proven cases. The portion of the CT scans performed on symptomatic patients is presented in red. d and e) The relationship between the side of pre-diagnosis abnormality and the side of mesothelioma development in histologically proven and clinically diagnosed cases.

from period A, 32 scans (for 25 patients) from period B and 23 scans (for 21 patients) from period C were analysed.

Abnormal pleural findings were seen in 58 (76%) scans (in 45 out of 61 scans of histologically proven cases and in 13 out of 15 scans of clinically diagnosed cases). These were divided between the three periods as follows: 20 out of 21 (95%) were positive in period A; 23 out of 32 (72%) were positive in period B; and 15 out of 23 (65%) were positive in period C. Figure 1a demonstrates the prevalence of different abnormalities in the three time periods for the histologically proven cases. A similar pattern was seen in the scans from patients with a clinical diagnosis. Figure 1b shows the side of the abnormality in comparison to the side of eventual disease development. Pleural plaques were more commonly seen in patients with previous documented asbestos exposure in similar proportions in both clinical and histologically diagnosed cases (present in 60% with positive exposure *versus* 23% of those with negative history). No considerable differences were noted in effusion and thickening.

Information on the indication for the scans was available in 72 of the 76 scans and the most common were extrapleural cancer staging or follow-up (16 scans, 22.2%), lung abnormality on chest radiography (15 scans, 20.8%) and persistent respiratory symptoms (14 scans, 19.4%). Patients complained of symptoms consistent with pleural disease in 20 (28%) scans. The relation between symptoms and abnormality was strongest in cases of effusion. 15 (65%) of the 23 patients with pleural effusion were symptomatic, whereas 14 (35%) of the 40 patients without effusion were symptomatic (Chi-squared 5.3, asymptotic significance 0.021). The relationship between symptoms and both thickening and plaques was weaker. There was no appreciable relationship between the subtype of MPM and the reported asbestos exposure or the pattern of CT abnormality.

The study cohort shows the typical demographic and clinical characteristic for MPM patients. The high prevalence of clinical diagnosis (23.4%) points to the late presentation of the disease in some patients and the challenge in obtaining diagnostic biopsies in others [2].

MPM development is causally related to asbestos exposure, and it is specifically seen in patients exposed at an early age [1]. However, it has been reported in patients without previous documented exposure [7]. The cumulative dose of exposure is not crucial to the development of MPM, as is the case with benign asbestos disease [1, 8]. In this study, 32% of patients did not report exposure to asbestos, which could be due to brief exposures that were subject to recall bias. The finding that pleural plaques were more commonly seen in those with documented exposure lends support to the notion that the development of plaques is related to long exposures.

The feasibility and usefulness of screening for early MPM is questionable [7]. In part, this is because the early appearances of mesothelioma on thoracic CT are not well characterised [9]. Additionally, it is not

known if early discovery of the disease affects prognosis [7]. While a large screening study of >1000 patients using low-dose CT failed to discover any MPM [10], another study demonstrated several new diagnoses of MPM on follow-up by observing for changing plaque morphology [9]. It was noted that in workers exposed to asbestos, and even after controlling for length of asbestos exposure, the presence of plaques was associated with an increased statistical risk of developing MPM [11]. However, the agreement in the mesothelioma community is that plaques are mostly regarded as a benign condition unrelated to MPM, and a marker of previous asbestos exposure [2, 12]. The other benign pleural manifestations (effusion and thickening) are also generally regarded as not associated with increased risk of MPM [8].

By comparing the side with the previous abnormality and the side with MPM development, the data in this study are concordant with the general agreement that plaques are not related to MPM development. A strong signal, however, was demonstrated between historical pleural effusion and MPM development. Pleural thickening was noted to be generally seen on the side of MPM development. Both effusion and thickening were noted on scans that predated diagnosis of MPM by more than a year.

In conclusion, it is difficult to infer a pattern of evolution of MPM from our data, but the presence of previous pleural effusion or thickening warrants careful follow-up. A few patients do not exhibit any abnormalities a few months before diagnosis while others carry pleural abnormalities for several years prior to a diagnosis of mesothelioma. This information might be of clinical relevance as lung cancer screening programmes, and CT scans in general, are used more widely across the UK.

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