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Title: CT abnormalities antedating mesothelioma diagnosis - a perspective on the natural history

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Take home message: 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.

To the Editor,

Malignant pleural mesothelioma (MPM) is an aggressive and fatal disease that typically presents with breathlessness, chest pain or both[1] and 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 between 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 are suspicious of MPM[3, 4], but none of these signs is specific enough to rule out other causes of pleural malignancy.

Additionally, 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 and 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 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: indication for each scan and the presence of pleural abnormalities (namely; effusion, thickening and plaques). CT scans were grouped into

three time periods: within one year prior to the diagnostic CT scan (period A), 1–3 years before diagnosis (period B), and more than 3 years before diagnosis (period C).

Out of 190 patients on the database, 47 had CT scans antedating the diagnosis of MPM. Eleven patients (23.4%) were diagnosed based on clinic-radiological basis either due to repeated negative biopsies or frailty precluding any invasive diagnostic testing. Thirty six patients (76.6%) were histologically confirmed (26 epithelioid, 6 biphasic, 3 sarcomatoid and 1 desmoplastic pathology). The median age of patients was 80 years (IQR 69 – 84 years) years and 11 patients (23.4%) had history of previous unrelated malignancy. Thirty nine patients (82.9%) were males, and previous asbestos exposure was documented in 32 patients (68%). The mean time from diagnosis to death in this cohort was 17.8 months (95% CI 11 – 24 m). For the epithelioid histology, mean survival was 22.8 m (95% CI 14-31 m), while with biphasic, it was 11.2 m (95% CI 4.8 – 17.5 m) and for clinical diagnosis 4.4 m (95% CI 1.9 – 7.6 m).

Seventy six pre-diagnosis CT scans were available for analysis. The mean time between a CT scan and diagnosis was 18 months (12 – 36, min 5m, max 109m). Twenty one scans (for 18 patients) 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 scans (76%) (in 45/61 scans of histology-proven and in 13/15 scans of the clinically diagnosed cases). These were divided between the 3 periods as follows: 20/21 (95%) positive in period A, 23/32 (72%) in period B and 15/23 (65%) 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 with the scans from patients with 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 with clinical and histological diagnosis (present in 60% with positive exposure vs. 23% of those with negative history). No considerable differences were noted with effusion and thickening.

Information on the indication for the scans was available in 72/76 scans and the most common were extrapleural cancer staging or follow up (16 scans, 22.2%), lung abnormality on CXR (15 scans, 20.8%) and persistent respiratory symptoms (14 scans, 19.4%). Patients complained of symptoms consistent with pleural disease in 20 cases (28%). The relation between symptoms and abnormality was strongest in cases of effusion. 15/23 of patients with pleural effusion (65%) were symptomatic whereas 14/40 of patients without effusion (35%) were symptomatic (Chi square 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 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 more than a thousand 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 of the previous abnormality and the side of MPM development, the data of this study is 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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Figure legends:

Figure 1: A Proportion of different pleural abnormalities in pre-diagnosis CT scans in the 3 time periods for histologically-proven cases. Portions of CT scans performed on symptomatic patients are presented in red. B Relation between side of pre-diagnosis abnormality and side of mesothelioma development in histologically proven cases (left) and clinically diagnosed cases (right).