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REVIEW

Non-Specific Pleuritis: An Update

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Abstract

Purpose of Review Non-Specific Pleuritis (NSP) is a common diagnosis following thoracoscopy and encompasses a broad range of aetiologies with heterogeneous outcomes. In this article, we review pathophysiology, associated syndromes, and current best practice in follow-up.

Recent Findings NSP typically runs a benign disease course; however, the biomechanical consequences of subsequent tissue re-modelling can be severe. A proportion of patients develop malignancy, notably pleural mesothelioma (PM), and clinicians currently lack the ability to stratify those at risk. Some may be harbouring occult malignancy with false-negative pleural biopsies. Alternatively, NSP may represent a true pre-PM precursor supported by the recent characterisation of mesothelioma-in-situ.

Summary Prospective surveillance of NSP patients could unlock the final biological milestone preceding PM evolution. Progress in this area would permit a more personalised patient stratification, whilst offering novel opportunities for translational research. The PREDICT-Meso International Accelerator Network has been established to focus on this goal.

Keywords Pleuritis · Non-Specific Pleuritis · Benign Pleural Inflammation · Pleural Effusion · Pleural Mesothelioma · Asbestos

Introduction

Pleuritis typically presents with a pleural effusion +/- pleural pain. Since there are over 60 recognised causes of pleural effusion, robust diagnostic assessment is essential. In this setting, thoracoscopy delivers optimal performance, reflecting access to full thickness pleural biopsies under direct vision [1, 2]. In patients without evidence of pleural malignancy, infection or active granulomatous disease, a broad range of histological features may lead to a clinical diagnosis of Non-Specific Pleuritis (NSP) [3]. Several specific aetiologies for NSP are recognised, including post-pleural infection, benign asbestos-related pleuritis, cardiac failure, various autoimmune pleuritides including rheumatoid arthritis, drug-induced pleuritis, post-coronary artery bypass grafting (CABG) and chronic uraemic pleuritis [3, 4]. The term 'Idiopathic NSP' should only be used after comprehensive investigation [3]. NSP is a common clinical label in specialist pleural services, with a typical incidence of around 40% following local anaesthetic thoracoscopy (LAT) [3]. The major clinical concern raised by NSP is the possibility of a missed specific diagnosis and treatment opportunity, including a missed cancer. NSP patients appear at risk of pleural malignancy in the short-to-medium term, most notably pleural mesothelioma (PM) [5–11]. This raises concerns regarding the need for further immediate investigations, and the most effective follow-up strategy. In this article, we review the pathophysiology of NSP, the common associated syndromes and best practice in surveillance and follow-up.

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Pathophysiology

In health, the pleural space contains a small volume of fluid, which is secreted by resident mesothelial cells, permitting smooth movement of the lung during the respiratory cycle [12]. Following insult or injury, the pleural mesothelium and

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its associated basement membrane also plays a critical role in orchestrating an inflammatory response, resulting either in effective clearance and appropriate healing or generation of a fibrous pleural matrix reflecting disequilibrium between fibrin generation and degradation [12]. In event of the latter, multiple pro-inflammatory and pro-fibrotic cellular pathways are implicated, with both mesothelial cells and infiltrating cells releasing inflammatory mediators, including vascular endothelial growth factor (VEGF), interleukin-8 (IL-8), monocyte chemotactic peptides (MCPs) and nitric oxide (NO) [4, 12]. Where chronic inflammation ensues, increased microvascular permeability permits efflux of pro-coagulant fluid into the pleural space with resultant initiation of the coagulation cascade and formation of fibrin [4]. VEGF appears to be a key mediator of pleuritis, and intra-pleural administration of anti-VEGF antibodies have been shown to decrease pleural fluid volume, IL-8 levels, and pleural adhesions in animal models [13, 14]. TGF-b regulates cell proliferation, differentiation, and extracellular matrix formation and once activated, will recruit fibroblasts, and suppress fibrinolysis [3, 12]; it is therefore a potent promotor of pleural fibrosis. In vitrostudies have recently demonstrated the capacity for mesothelial cells to undergo epithelial-to-mesenchymal transition (EMT), contributing to this process [15].

Where pleural inflammation and fibrin deposition persist, the pleural space will be progressively re-modelled, resulting in biomechanical changes, including formation of adhesions and non-expansile lung (NEL) [12]. NSP may be diagnosed at any point of this progressive remodelling process, which explains the diverse histological features compatible with the diagnosis. Karapathiou et al. recently reviewed 100 NSP cases and associated histological phenotypes with aetiology. The most common pattern was inflammatory (40%), followed by fibrinous (14%), septated (8%) and haemorrhagic (2%) [16]. In this study, severely fibrotic pleura with vascular proliferation and neutrophils was closely associated with bacterial infection, whilst severe, lymphocyte-rich fibrosis was more common in autoimmune disease [16]. Viral and cardiac aetiologies were associated with milder fibrosis. This data highlights the need for more robust stratification of NSP through application of modern tools for histomolecular classification.

Clinical Syndromes

Benign Asbestos Pleural Effusion

Asbestos fibres are a well-documented source of pleural inflammation and may result in acute pleuritis, which typically presents within 10 years of exposure. However, bans on asbestos utilisation in many developed nations mean acute asbestos pleuritis is now rare. Later presentations are common (30–50 years after exposure) with typical features including an exudative effusion that may be blood-stained and contain a mixture of lymphocytes, mesothelial cells and/or eosinophils [12]. In this setting, careful exclusion of PM is of critical importance, with minimum investigations ideally including venous-phase contrast-enhanced CT scanning and thoracoscopy [1]. Most cases of BAPE will run a benign disease course, however a period of surveillance is essential given the risk that PM will emerge over the next 1–2 years [5]. In a recent systematic review and meta-analysis, the risk of PM evolution following a diagnosis of NSP was 5.44%(95% CI 3.37–7.51), with significant heterogeneity ($p < 0.001$, I^2 82.7%) across 17 studies describing 2607 NSP cases and 146 PM evolutions [17]. In this study, higher PM evolution rate was associated with asbestos exposure by cohort and high PM incidence settings, where the risk was 14.9% and 11.4% respectively [17]. This meta-analysis included data from the recently published UK multi-centre Meso-ORIGINS Feasibility study, in which histologically-confirmed PM evolution was observed in 36/257 NSP patients (14% (95% CI 10.3–8.8%)) [6].

It is unclear whether NSP represents a genuine precursor to PM or reflects false negative sampling in patients with radiologically and thoracoscopically occult disease. The latter is certainly plausible, at least in some patients, given various challenges in securing a diagnosis of PM. PM tumours are highly stromal making both biopsy acquisition and histological assessment difficult. PM is further characterised by considerable anatomical and intra-tumour heterogeneity (ITH), with multiple synchronous tumours typically interspersed between areas of non-malignant inflamed or fibrotic pleura [18, 19]. The huge surface area of the pleura (typically 4000 cm^2 in an average 70 kg male) places a premium on complete inspection via thoracoscopy and repeat sampling should be considered where the pre-test probability of PM is considered high [1, 20]. The recently reported TARGET trial failed to demonstrate any additional benefit from PET-directed re-biopsy in this setting, although the study was underpowered due to below-target recruitment [21].

The possibility of NSP being a true precursor to PM is supported by multiple studies. Harber et al. [22] advocate a model of immune mediated carcinogenesis, triggered by decades of pleural inflammation. They hypothesise that failed clearance of asbestos fibres by phagocytic macrophages results in 'frustrated phagocytosis', continuous amplification of proinflammatory cytokines and a permissive milieu which drives mesothelial cell proliferation and mutation [22]. Asciak et al. recently reported that growth of pleural effusion derived cancer cell lines was potentiated by use of effusion as a cell medium [23], building on prior data from Hegmans et al. reporting that PM effusions contain a variety of pro-tumour and immunosuppressive mediators [24]. Such

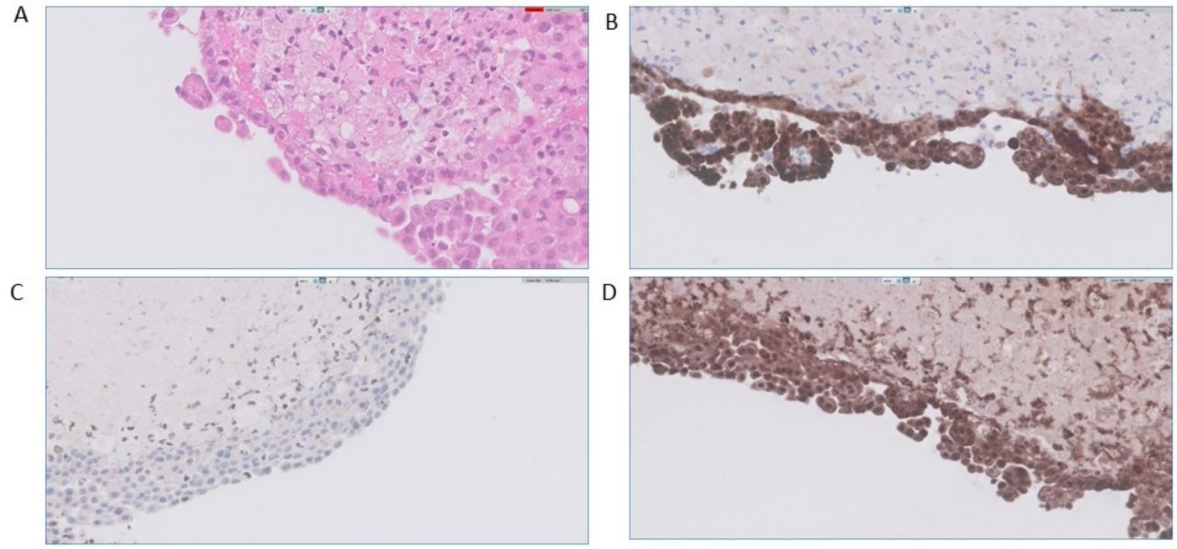

Fig. 1 Mesothelioma-in-situ Histology. **A**: Magnification X100 H&E stained section of pleural biopsy showing surface mesothelial cells with mild pleomorphism and a focal papillary architecture. **B**: Magnification X100 Calretinin antibody stain showing nuclear and cytoplasmic staining within the mesothelial population. **C**: Magnification X100 BAP 1 antibody stain showing loss of nuclear staining within the atypical mesothelial cells. **D**: Magnification X100 MTAP antibody stain showing retention of expression within the mesothelial cells and background inflammatory cells

a thesis is supported by observations of increasing PM risk with increasing time after exposure, which varies from other environmental cancers, where risk commonly decreases with time [25]. Potential mediators of BAPE to PM evolution are likely to be multifactorial and highly complex. In this setting, the occurrence of asbestos-associated NSP offers a unique window-of-opportunity for translational research. The PREDICT-Meso international accelerator network has been funded by CRUK to capitalise on this and is currently collecting a large cohort of longitudinal tissue samples spanning the time course of asbestos-associated NSP (or apparent BAPE) and PM evolution. This material is being used to target identification, for generation of new pre-clinical models and for drug screening.

Mesothelioma-in-Situ

A number of solid tumours have a described in-situ phase where pre-malignant detection might permit early intervention. Mesothelioma-in-situ (MIS) was first described by Whittaker et al. [26] in 1992 based solely on morphological features. The definition included a single layer of papillary projections of cytologically atypical mesothelial cells [26]. However, the original cohort described had co-existing invasive PM and it was not until 2021 that the WHO recognised MIS and a distinct pathological entity [27, 28]. This increased confidence reflected considerable progress in the characterisation of the PM tumour genome, which is typified by a low mutational burden dominated by inactivation of tumour suppressor genes, including cyclin-dependent kinase inhibitor 2 A (CDKN2A), BRCA1 associated protein 1 (BAP1) and Neurofibromin 2 (NF2) [29]. Loss of CDKN2A and BAP1 can be detected by routine laboratory technique [27, 28], providing enhanced diagnostic capability for PM and therefore for definition of MIS in selected patients, summarised in Fig. 1.

- BAP1 is a gene with complex functionality including DNA damage repair, gene expression regulation, and chromatin remodelling [30]. Using whole exome sequencing, Dacic et al. [31] recently reported that MIS development is associated with somatic mutations in BAP1 and surmise that loss of gene expression represents an early event in malignant transformation. A recent meta-analysis by Wang et al. [32]reported a sensitivity and specificity for BAP1 immunohistochemistry (IHC) for PM of 56% (95% CI, 50–62%) and 100% (95% CI, 95–100%), respectively.
- CDKN2A is responsible for production of the cell cycle inhibitor protein p16(INK4A) with an additional indirect effect on the expression of the paradigmatic tumour suppressor gene p53 [33]. Wu et al. [33] examined CDKN2A expression in cohort of PM cases via p16 FISH and found homozygous deletion in 10/18 (55.6%) epithelioid and 22/22 (100%) of sarcomatoid cases. They concluded that using a cut-off value for homozygous deletion of 14.4%, p16 FISH will reliably differentiate PM from benign fibrous pleuritis [33, 34]. Wu et al. [33] also reported

hypermethylation of the p16 gene in 3/7 (42.9%) benign fibrous pleuritis cases, postulating a possible role in tumorigenesis.

- MTAP is an enzyme involved in purine metabolism. The gene encoding MTAP is located close to CDKN2A at the 9p21.3 locus and is co-deleted in 74% of cases [35]. MTAP IHC is commonly used as a surrogate marker for p16 FISH, with the combination of MTAP and BAP1 IHC recently reported by Hida et al. [35] to offer 76.5% sensitivity and 100% specificity for differentiation of PM from reactive mesothelial hyperplasia.

The 2021 WHO criteria for a diagnosis of MIS incorporate these data and include [1] a non-resolving pleural effusion [2] absence of thoracoscopic or imaging suggestive of pleural malignancy [3] a single layer of mesothelial cells on the surface without stromal invasion [4] loss of BAP1 and/or MTAP and/or CDKN2A homozygous deletion and [5] MDT input [28]. Given the novel nature of MIS, precise management and prognostic implications have not been fully established. A recent survey of 34 pulmonary pathologists highlighted inconsistency regarding how the diagnosis of MIS is applied by experts internationally and the true prevalence of MIS is therefore unknown [36]. In a cohort of 10 MIS patients, Churg et al. [27] reported invasive PM in 70% of cases with a median of 5 years to progression. As the research landscape evolves, the relationship between MIS and NSP should become more apparent, including improved risk stratification and opportunities for early intervention in those at very high risk of subsequent PM. These studies are currently being conducted via the PREDICT-Meso international accelerator network.

Diffuse Pleural Thickening

Asbestos related pleural fibrosis can be discrete (pleural plaques) or diffuse, and in the latter setting may meet the diagnostic criteria for Diffuse Pleural Thickening (DPT) [12, 37]. DPT has several aetiologies, however asbestos exposure is the most prominent association [12]. DPT risk appears to directly correlate with the cumulative dose of exposure, which is not true of pleural plaques [38, 39]. DPT may progress from BAPE, reported in 27% of cases, or represent an extension of interstitial fibrosis [38]. DPT is typically unilateral with a predilection for the costophrenic recess, however it can be extensive encompassing the entire lung [12, 37]. Unlike pleural plaques, DPT typically involves the visceral pleura and where subsequent adhesions to the parietal pleural develop, may result in obliteration of the pleural space [12].

In the UK, the definition of DPT is set by the Department for Work and Pensions for adjudication of Industrial Injuries Disability Benefit. This is based on CXR findings, requiring both obliteration of the costophrenic angle and either unilateral or bilateral pleural thickening [37]. The key differential diagnosis is PM, which ultimately requires histological differentiation. The treatment of DPT is supportive, and to date there are no high-quality trials of specific interventions. Surgical decortication is biomechanically plausible as a strategy in severe cases, but if considered should be prefaced by careful exclusion of any parenchymal disease that may be contributing to symptoms and might preclude lung re-expansion [12]. Decortication is unlikely to be successful in cases with concomitant interstitial fibrosis although more research is urgently needed [12].

Pleural Infection

The incidence of pleural infection is increasing, with currently 11.2 cases per 100,000 of the UK population per year [40]. Pleural infection is defined as bacterial entry and replication in the pleural space whilst the term empyema is reserved for the macroscopic detection of purulent pleural fluid or positive pleural culture. If not managed appropriately, bacterial empyema can result in obliteration of the pleural space, with subsequent adhesions, retention of infected material and pleural fibrosis. Accordingly, pleural infection is a common diagnosis associated with a histological label of NSP [3]. The current standard of care for pleural empyema is prolonged antimicrobial therapy alongside pleural drainage via an intercostal chest drain [40]. However, conservative management is often insufficient where extensive pleural organisation has already transpired [40–42]. Maskell et al. [42] reported that the mortality from pleural infection was 20% and approximately one third of cases required surgical referral. Early drainage of the pleural space is a critical step in the management of pleural infection. Intra-pleural enzymes are now routinely administered following the MIST-2 RCT, which demonstrated significantly shorter hospital stay and reduced risk of surgical referral with the combination of tissue plasminogen activator (tPA, a fibrinolytic) and DNase (a mucolytic that reduces fluid viscosity) [41]. Subsequent observational studies have reported similar success rates to the original MIST-2 trial, and equivalent efficacy with a reduced dose of tPA, thereby reducing cost and the potential for adverse events [40, 43]. This evidence has been reflected in recently published BTS guidelines for management of pleural infection [40]. Malignancy can co-exist with pleural infection and synchronous disease processes are reported in up to 5% of cases [40]. In this context, the presence of a mass involving the extra pleural fat and/or mediastinal pleural thickening may be suggestive markers, however recommended practice is to perform surveillance imaging for up to two years to exclude occult malignancy, particularly in the presence of persistent symptoms and/or risk factors [40].

Rheumatoid Arthritis

Rheumatoid pleural effusions can occur before, concurrently with, or following the onset of arthritis [44]. RA should be considered in all undiagnosed pleural effusions regardless of pre-existing joint disease [44]. A historical post-mortem series reported pleural involvement in up to 50% of patients with rheumatoid disease [45]. Most rheumatoid pleurisy cases are indolent, with minimal symptom burden and a self-limiting disease course [44, 46]. Patients with persistent, symptomatic rheumatoid effusions can be challenging to manage and sequential aspirations are not recommended due to the higher risk of infection in this immunocompromised cohort [12]. Rheumatoid pleural effusions are more common in older males and patients with rheumatoid nodules and/or serum rheumatoid factor positivity [46, 47].

In cases of refractory rheumatoid pleuritis, pleural fibrosis may ensue and can lead to a fibrous peel with subsequent NEL. Decortication may be considered if patients are symptomatic [12, 46]. In a historical case series of 19 patients with a rheumatoid effusion, only one developed severe pleural fibrosis requiring decortication [48]. In this cohort, two patients received oral corticosteroids and the effusion resolved shortly afterwards, however, further studies have not replicated this finding [12]. Accordingly, there are no established protocols for the management of symptomatic rheumatoid pleural effusion and further research is urgently required, particularly given recent successes in the treatment of joint disease using DMARDs. Of note, there are several case reports showing effectiveness with the use of abatacept and tocilizumab in refractory cases of rheumatoid pleurisy [12, 49].

Post CABG Effusion

Coronary Artery Bypass Grafting (CABG) remains the most common cardiothoracic surgical procedure performed globally. Pleural effusions are common following CABG, reported in up to 85% of cases [50, 51]. Effusions are typically small, left-sided, and transient, however, in a minority of patients the effusion can persist with resultant pleural fibrosis [12, 51]. Lee et al. [51] described the clinical course and pleural biopsy findings in eight patients who underwent thoracoscopy or thoracotomy for refractory post-CABG effusions. Histological changes appeared to develop over time, with longer intervals (> 6 months post-CABG) revealing less inflammation and more fibrosis. They concluded that where a large post-CABG pleural effusion persists (for > 6 months), decortication should be considered to prevent effusion recurrence [51]. The future incidence of post-CABG pleural fibrosis will likely correlate with the future frequency of CABG and recent successes with multi-vessel percutaneous coronary intervention may see numbers fall [50].

Drug-induced Pleuritis

Drug-induced pleural disease is less common than drug-induced parenchymal disease, but the two can co-exist [12]. A wide array of drugs have been associated with NSP, including Nitrofurantoin, Amiodarone, Bromocriptine and various chemotherapy agents. Given the current frequency of new drug licensing, the incidence of drug-induced pleuritis needs continuous careful surveillance. Consideration of drug-induced phenomena is essential in the diagnostic work up for an undiagnosed pleural disease and is often overlooked [52, 53]. Drug-induced pleural effusions are typically eosinophilic; however, this is not pathognomonic [53]. Withdrawal of the causative agent remain the cornerstone of management although a degree of pleural thickening may persist, mandating careful follow-up [12].

Surveillance of NSP

The majority of NSP diagnosis will follow a benign disease course; however, given the discussed association with PM evolution, careful follow-up and selected repeat biopsy are of critical importance. Current expert consensus would advocate NSP surveillance for 2 years with the risk of malignant progression thought to be highest in the first 6 months. This was supported by the Meso-ORIGINS Feasibility study which reported a median time to repeat biopsy of 3.5 months (IQR 2–9.5) [6]. In the largest series on NSP to date, Reuter et al. [5], demonstrate the number needed to follow up (NNF) was 18, to identify one malignancy in the first year of follow up, becoming less effective with time, with a reported NNF of 260 between years 1 and 3. However, malignant progression has been reported in cases up to 64 months and clinicians need improved guidance to effectively communicate this risk and personalise management plans. Ferguson et al. [6] used multivariable logistic regression to interrogate baseline features of a multi-centre NSP cohort. They demonstrate that that age (OR 1.06 (95% CI 1.02 to 1.12)) and malignant CT features (OR 4.78 (95% CI 2.36 to 9.86)) were the only findings independently associated with PM evolution.

Non-Invasive Biomarkers

The generation of a robust, non-invasive biomarker which can stratify risk in an NSP cohort remains an unmet clinical need [54]. Identified biomarkers will require high sensitivity and specificity given the low incidence of PM in most settings. Extensive efforts to identify a suitable serum biomarker have been made to date with conflicting results [55–58]. However, in a recently published prospective study, the SOMAscan proteomic assay reliably differentiated PM

from asbestos exposed controls with 75% sensitivity, and 88% specificity providing an area of interest [54]. In the Mesobreath studies, an exhaled breath volatile organic compound signature based on gas chromatography-mass spectrometry discriminated PM from asbestos-exposed controls with 100% sensitivity and 91% specificity [59, 60]. These risk profiling inputs are being collected within the PREDICT-Meso Accelerator Network.

Imaging

Whilst it is entirely intuitive that malignant CT findings are independently associated with a diagnosis of PM, radiological differentiation remains limited by tumour morphology where overt pleural tumour is often occult. This is particularly true in early-stage PM where extra-pleural malignant features are frequently absent [61]. Tsim et al. [61] report that 40% of initial contrast-enhanced computed tomography (CT) scans were reported as "benign" in patients with subsequently confirmed PM, highlighting the limitations. The BTS pleural guidelines advocate that thoracic ultrasound (TUS) is performed for every patient presenting with an effusion and again whenever a pleural procedure is being performed [40]. Identification of pleural thickening on TUS has been correlated with an eventual malignant diagnosis, with diagnostic accuracy capable of exceeding that of CT. A growing body of evidence also supports use of MRI in distinguishing benign from malignant pleural disease [62–65]. Malignant pleural thickening will typically show inhomogeneous hyperintensity on proton-density T2-weighted images and enhancement on T1-weighted images following gadolinium injection, in contradiction to benign disease that is of low signal on both sequences [65]. When these signal characteristics are combined with morphology and a pleural thickening > 1 cm, the accuracy of MRI is very high for diagnosing malignant pleuritis with sensitivity of 100% and specificity of 95%. As well as identifying morphological features, MRI can provide functional information via the use of methods including diffusion-weighted imaging or dynamic contrast enhancement [62, 63]. The latter exploits the pathognomonic increase in blood vessel density, typical of tumours, in the context of neo-angiogenesis [62]. Such imaging modalities have been used with success to differentiate malignant from benign breast and prostate lesions.

Conclusions

NSP remains a challenge for clinicians encompassing a broad range of aetiologies with heterogeneous outcomes. Establishing any clear aetiology for NSP is the clinical priority in all patients. Most patients experience a benign disease course; however the biomechanical consequences of chronic inflammation, fibrosis and subsequent pleural space re-modelling may be significant in some. Despite the well documented risk of malignant evolution clinicians currently lack the ability to confidently differentiate between patients with true benign disease from those who will progress, and similarly those who will progress quickly compared with those who will progress slowly. Improved understanding in this area would permit a more personalised follow-up plan with less uncertainty for patients involved. The recent characterisation of MIS supports the notion that NSP represents a genuine PM pre-cursor and opens novel avenues for early intervention. Prospective surveillance of NSP patients from a pre-PM timepoint could unlock the final biological milestone preceding disease evolution. The PREDICT-Meso International Accelerator Network has been established to focus on this goal.

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Conflict of Interest KGB declared institutional grant funding from Rocket Medical and RS Oncology, lecture honoraria from Bristol-Myers Squibb and is Chief Investigator of the PREDICT-Meso International Accelerator Network.

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