

Inflammation in malignant mesothelioma - friend or foe?

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Submitted Sep 13, 2012. Accepted for publication Oct 17, 2012.

DOI: 10.3978/j.issn.2225-319X.2012.10.02

Introduction

The relationship between inflammation and cancerous growth has been extensively investigated over the past 150 years. Following Virchow's identification of leukocytes within neoplastic tissue in 1863 (1), the role of inflammatory cells and pathways in the pathogenesis of a variety of tumour groups has become well established. In a variety of malignancies, environmental and infective agents are seen to play critical roles in the production of tissue damage and inflammatory reactions. Furthermore, cytokines, chemokines and angiogenic factors produced in chronic inflammatory states provide a microenvironment favourable for cellular survival and angiogenesis (2). Cytokines such as interleukin (IL)-6, IL-10 and IL-17/23 are postulated to be at the centre of a signalling network, activating pathways such as STAT3 or NFκB (3). In the case of malignant pleural mesothelioma (MPM), asbestos fibre exposure occupies this central pathogenic role, and the ensuing alteration of immune-competent cells may result in a decline in tumoral immunity (4).

The mechanisms by which inflammatory processes impact on the development of MPM remain incompletely understood, and are beyond the scope of this review. However, there is an increasing awareness of the relationship between the degree of both local and systemic inflammatory response and the prognosis of patients with MPM. We hereby review the available evidence on the impact of inflammation on survival in patients with MPM and examine the potential therapeutic implications.

Local inflammation

The relationship between the degree of inflammatory infiltration in tumours and patient prognosis has been

recognised in several malignancies. In colorectal cancer, the presence of intratumoral immune cell infiltrates, and markers of T cell migration, activation and differentiation, were both associated with reduced early metastatic invasion, early stage disease and improved prognosis (5). The presence of intratumoral T cells was also noted to be correlated with improved survival in epithelial ovarian cancer, with associated increases in expression of interferon-gamma, IL-2, and with lymphocyte-attracting chemokines within the tumour (6).

Similar inflammatory mechanisms have also been identified in MPM. A report of 58 biopsy specimens by Leigh *et al.* noted the presence of a marked variability of lymphocytic infiltration, with prolonged survival associated with an enhanced presence of lymphoid cells (7). More recently, histological assessment of specimens from 175 patients with MPM presenting with an epithelial subtype analysed the inflammatory status of the tumour (defined as tumour nests containing tumour cells and intratumoral stroma) and surrounding stroma (defined as cells adjacent to the tumour nest) (8). In this study, acute inflammatory response was defined as the presence of neutrophils while chronic inflammatory response was defined as the presence of lymphocytes and plasma cells. Patients with a marked chronic inflammatory response in the stroma demonstrated improved survival in comparison to those with a low response (median overall survival 19.4 vs. 15.0 months; $P=0.01$), and a chronic inflammatory response in the stroma remained an independent predictor of survival on multivariate analysis (HR=0.659; 95% CI: 0.464-0.937, $P=0.02$) (8). However, acute and chronic inflammatory responses in the tumour coincided with vascular invasion, a known predictor of reduced survival. It is important to note that no significant impact on survival was identified in relation to acute or chronic tumoral inflammatory changes or in acute stromal

changes within this study. Furthermore, this study did not provide phenotypes of the immune cells examined.

The observation of a more favourable prognosis associated with the presence of lymphocytic infiltrates was also shown in two independent series of MPM patients undergoing the radical surgical procedure extrapleural pneumonectomy (EPP). Both studies suggested that high levels of tumour-infiltrating CD8⁺ lymphocytes were associated with an improved survival on multivariate analysis (HR=0.27-0.38; P<0.05) (9,10).

Immunohistochemical analysis of the types of the immune cells present in tumour samples revealed a significant population of macrophages (11). In non-epithelial tumours, approximately 27% of the tumour area was comprised of macrophages, and the presence of macrophage was negatively correlated with survival (P=0.008). This unique finding could not be replicated in epithelial tumours (P=0.7). The majority of the macrophages possessed an immunoregulatory phenotype (M2), responsible for the production of cytokines such as IL-10, and suppression of immune reactions.

The methods by which such cellular changes developed were investigated by Hegman *et al.*, who analysed cytokine expression in mesothelioma cell lines and effusions via immunohistochemistry (12). Vascular endothelial growth factor, angiogenin, transforming growth factor- β , and epithelial neutrophil-activating protein ENA-78 associated with immune suppression, angiogenesis and plasma extravasation were detected in cell cultures and pleural effusions. In contrast, hepatocyte growth factor, macrophage inflammatory protein (MIP)-1 δ , MIP-3 α , neutrophil activating peptide (NAP)-2, and pulmonary and activation regulated chemokine (PARC) were present only in pleural effusion, suggesting that they were secreted by stromal and inflammatory cells.

From the available evidence, it appears that there is a complex interaction between immune infiltrates and other cell types, both within the tumour and in the stroma. There is consistent evidence that a high infiltration of lymphocytes (especially CD8⁺ T cells) is associated with a survival advantage in patients with MPM. In contrast, an increased presence of macrophages of the M2 phenotype within the tumour is associated with a poorer prognosis in non-epithelial MPM.

Systemic inflammatory response

The impact of inflammatory pathways extends beyond a

simple role in the pathogenesis of MPM and can contribute to many of the systemic symptoms commonly noted in patients with advanced MPM. Constitutional symptoms suggestive of an increased systemic inflammatory response occur in approximately 30% of patients with MPM and include fever, weight loss, fatigue and night sweats (13). These symptoms are typically associated with more advanced disease and increased resistance to chemotherapy (14). It has also been shown that patients with MPM experiencing systemic symptoms often have a less favourable prognosis (15-17).

In addition, there has been early evidence suggesting the prognostic importance of systemic inflammatory response in patients with MPM, with leucocytosis, thrombocytosis, and elevated lactate dehydrogenase (LDH) being included in composite scoring systems such as the European Organisation for Research and Treatment of Cancer (EORTC) and the Cancer and Leukemia Group B (CALGB) systems (18,19). These observations were validated in an analysis by Tanrikulu *et al.*, which included 363 Turkish patients with MPM. This study reported that in addition to poor performance status, pleural fluid glucose level ≤ 40 mg/dL and presence of pleural thickening, an elevated LDH > 500 IU/L (HR=2.24; 95% CI: 1.585-3.168; P=0.001) and platelet count $> 420 \times 10^3$ / μ L (HR=1.33; 95% CI: 1.009-1.757; P=0.043) were associated with reduced median survival on multivariate analysis (20).

The above prognostic assessments highlight a growing emphasis on inflammatory biomarkers in determining the prognosis of MPM. In recent years, the blood neutrophil-lymphocyte ratio (NLR) has been identified as a prognostic marker in a number of malignant and non-malignant conditions. It is calculated simply from the full blood count by dividing the number of neutrophils by the number of lymphocytes. Early reports demonstrated a role for the NLR in predicting adverse outcomes in patients critically ill with sepsis (21) and in those requiring coronary intervention (22,23). More recently, within a wide range of malignancies, including pancreatic (24), colorectal (25), and gastric carcinomas (26), an elevated NLR has been demonstrated to be an independent predictor of higher stage disease and reduced survival, with predictive power superior to total white cell, neutrophil or lymphocyte counts alone.

The association between MPM and NLR was first identified in a study involving 173 patients who underwent systemic therapy. In this report, patients with high baseline NLR (≥ 5) were independently associated with reduced overall survival (HR=2.7; 95% CI: 1.8-3.9; P<0.001) on multivariate analysis (27). This observation has been

validated in a cohort of patients undergoing EPP (HR=1.79; 95% CI: 1.04-3.07; P=0.04 for NLR \geq 3) (28) as well as in other retrospective series (HR=2.0-3.6) (29-31). Furthermore, it has been demonstrated that patients whose abnormal baseline NLR normalised after one cycle of systemic therapy had a significantly improved survival compared with patients whose NLR remained high (7.8 vs. 5.0 months; P=0.03) (27). Interestingly, a subgroup of patients with a low NLR in the study conducted by Suzuki *et al.* showed a trend towards better survival (18.9 vs. 10.1 months; P=0.34) (8).

Peripheral monocyte counts have also been associated with the prognosis of patients with MPM. Burt *et al.* identified a significant increase in monocyte counts (580 vs. 520 cells/ μ L; P=0.002) in non-epithelial versus epithelial tumours (11). Furthermore, higher monocyte counts correlated with advanced tumour stage non-epithelial tumour subtype, and reduced survival (HR=3.64; 95% CI: 2.25-5.80; P<0.0001) in all patients with MPM.

In addition to variations in blood cell populations, proteins associated with inflammatory status are elevated in numerous cancers. C-reactive protein (CRP), an acute phase reactant, has been noted to be significantly elevated in patients with metastatic disease across a variety of solid organ and hematological malignancies, including MPM. (32-34) In a retrospective study of 115 patients with a pathologically confirmed diagnosis of MPM, elevated CRP (\geq 1 mg/dL) was shown to be an independent indicator of poor prognosis (HR=2.07; 95% CI: 1.23-3.46; P=0.001) (35). Furthermore, an interaction between CRP and treatment modality was noted, in which patients with a normal CRP level who underwent EPP within multimodality therapy was associated with a significantly improved survival compared to non-surgical therapies (HR=7.26, 95% CI: 3.40-15.49; P<0.001). However, this observation was not evident in patients who underwent radical surgery with an elevated CRP (HR=0.911; 95% CI: 0.53-1.58; P=0.74). The prognostic role of CRP in patients with MPM was further validated study referenced earlier by Tanrikulu *et al.*, in which an elevated level of >50 mg/L was significantly associated with poor prognosis on multivariate analysis (HR=1.56; 95% CI: 1.139-2.105; P=0.005) (20).

Hypoalbuminaemia has also demonstrated prognostic significance for a variety of medical, surgical and oncological conditions, potentially reflecting a decline in nutritional status in addition to systemic inflammation (36-39). In their cohort of 278 patients admitted for palliative surgical intervention for MPM, Pilling *et al.* demonstrated albumin <35 g/L to be independently associated with a decline in survival

(HR=2.415; 95% CI: 1.70-3.44; P<0.0001) (40). This was consistent with previous findings of a significant decline in 3-month mortality in patients undergoing pleurodesis for malignant effusions (of all malignant causes) (41).

Expanding upon these biochemical observations, the modified Glasgow prognostic score (mGPS) - calculated by incorporating the presence of elevated CRP or hypoalbuminaemia - has been identified as an important measure of systemic inflammation. Within a number of malignant and non-malignant conditions, including metastatic breast and advanced gastro-oesophageal cancers (42,43), the mGPS has been identified as a significant prognostic factor. Assessment of the mGPS in MPM has revealed its strength as a biomarker. In multivariate analysis, mGPS was superior to both CRP and albumin alone (HR=2.6; 95% CI: 1.6-4.2; P<0.001) (31).

Thus, there is compelling evidence that a pronounced systemic inflammatory response is associated with poorer prognosis, and that tumour-derived cytokines can affect immune reactions peripherally in the bone marrow as well as locally within the tumour. It has been shown that mesothelioma cells and cell lines produce IL-6 (44-46), and a clinical study of 25 patients with MPM demonstrated that IL-6 present in pleural fluid could leak into the systemic circulation, thereby inducing clinical inflammatory reaction responses (47). However, it is unlikely that a single cytokine is responsible for the exaggerated systemic inflammatory responses observed in MPM patients, but rather, a complex interaction of pro-inflammatory cytokines, growth factors and anti-inflammatory cytokines exists.

Potential clinical impact

Prediction of treatment outcome

Despite a modest prolongation of survival by the platinum/pemetrexed combination, the prognosis of MPM remains poor (48). The identification of a simple but accurate prognostic factor, such as NLR, will enable clinicians to select patients who are most likely to benefit from the intensive therapeutic regimen, and avoid futile treatments in unsuitable candidates.

Based on the available evidence, local and systemic inflammatory markers have the potential to become valuable biomarkers. However, as for any biomarker, quantitative determination of clinically useful cut-off values requires further study and validation before inflammatory markers can be definitively introduced into routine clinical practice. This seems a feasible task, considering the varying levels of

NLR and CRP proposed in different studies, and a recent large review of NLR in cancer patients suggesting that a value of 4 may be appropriate (49).

Early recognition of chemotherapy futility

The normalisation in NLR after the first cycle of chemotherapy is strongly predictive of benefit from chemotherapy. One study suggested that failure of the NLR to return to normal (<5) after one cycle of systemic therapy was associated with poor response to treatment and significantly reduced overall survival (27). Although this observation has not been validated in other MPM studies, comparable observations have been reported in colorectal and lung cancer patients (25,50). It is not clear, however, whether the failure of the NLR to normalise in MPM is due to chemo-resistance or simply the result of inadequate dosing of chemotherapy. The clarification of this point will have significant impact on the potential therapeutic strategies for patients in whom the NLR does not normalise with chemotherapy.

Identification of patients at risk of developing cachexia

Progressive weight loss, anorexia, metabolic disturbance, asthenia, fat depletion and severe loss of skeletal muscle protein (sarcopenia) are key clinical features of cancer cachexia, affecting a significant proportion of patients with MPM. Although cancer cachexia is a well-recognised phenomenon, the exact diagnostic criteria are still controversial. However, inflammatory markers, such as CRP, have been increasingly incorporated or taken into account in the new diagnostic criteria of cachexia and pre-cachexia. The recognition of the importance of systemic inflammation in the development of cachexia will hopefully translate into earlier interventions to ameliorate this process.

Immunotherapy

The growing body of evidence supportive of an inflammatory component to the pathogenesis and prognosis of MPM highlights the need for research into immuno-modulatory therapies in this malignancy. Previous research at pre-clinical and clinical levels into targets including IL-2, IFN- γ and a number of co-stimulatory molecules have provided a promising impact upon immune response, but thus far failed to produce any significant effect on disease progression and prognosis (51). Based on the existing literature, there is a rationale for investigating immune therapy that promotes

lymphocyte infiltration in this disease. Furthermore, targeting the macrophage response may present a potentially new therapeutic approach, whereby promoting M1 phenotype, rather than the M2 phenotype typically seen in MPM, may restore anti-tumour immunity.

Immunotherapy related to mesothelioma can be categorized into passive and active pathways (52). Passive immunotherapy in the form of anti-mesothelin monoclonal antibodies used in the treatment of mesothelioma include amatuximab, which failed to demonstrate significant radiological responses when given alone, but may be effective as an adjuvant therapy with chemotherapeutic regimens (53,54). Active immunotherapeutic approaches to elicit CD4⁺ and CD8⁺ T-cell responses to mesothelin and Wilms tumour-1 have been under investigation using a novel peptide vaccination called TroVax (55).

Conclusions

It is apparent that inflammatory biomarkers can provide valuable prognostic information in patients with MPM. It has been shown that, in the local tumour environment, certain inflammatory infiltrates such as CD8⁺ T lymphocytes are associated with an improved prognosis, whilst others, such as M2 macrophages, are associated with poorer survival. There is consistent evidence to suggest an association between a systemic inflammatory response, represented by elevated CRP and NLR, and poorer prognosis. Therefore, the location and the type of inflammatory response have an impact on the overall prognosis of patients with MPM.

However, it must be emphasised that prospective validation of potential inflammatory biomarkers is required before they can be incorporated into clinical practice. In terms of potential therapies, "anti-inflammatory" therapeutics hold great promise, with the aim of inducing an anti-tumour effect or suppressing angiogenesis, by dampening the systematic inflammatory response and targeting the local response within the MPM tumour. Taken together, recent advances in our understanding of the roles of the immune system and the inflammatory response in MPM provide the rationale for further investigation in this field.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Linton A, van Zandwijk N, Reid G, Clarke S, Cao C, Kao S. Inflammation in malignant mesothelioma - friend or foe? *Ann Cardiothorac Surg* 2012;1(4):516-522. DOI: 10.3978/j.issn.2225-319X.2012.10.02