Correspondence

Malignant mesothelioma and erionite exposure

To the Editor:

We have read the review entitled "Malignant pleural mesothelioma" by Boutin et al. [1] with great interest. In contrast to the situation in industrialized Western countries in which mesothelioma is mostly related to previous occupational exposure to asbestos, it is rather associated with environmental exposure to tremolite asbestos in central and eastern Turkey [2-4]. There are several asbestos deposits in the rural areas in these regions. Despite its lack of economic value, asbestos contaminated soil (white soil) was widely used by the villagers both for insulation on the roofs and as plastering material for the walls of houses in the past [1, 2]. Thus, long-lasting, usually with the onset of exposure at birth, indoor exposure has occurred in these villages. The prevalence of pleural plaques radiologically detected among persons >20 yrs of age range 0.2-24% in these villages [1, 4]. In mesothelioma patients with environmental asbestos exposure, the geometric mean of the asbestos body concentration in bronchoalveolar lavage (BAL) was 5.8 bodies·mL⁻¹ met in comparison to 0.22 bodies·mL⁻¹ for unexposed control patients [5]. The local use of asbestos-contaminated soil has declined with improving socioeconomic conditions, but has not totally ceased [4].

Another mineral, a natural fibrous zeolite named erionite, is also implicated as the cause of mesothelioma in three specific villages (Karain, Tuzkoy and Sarthidir) in central Turkey [6, 7]. The article by Baris et al. [7] which is cited in the review [5] is also related not to asbestos exposure as referred to by Boutin et al. [1], but to environmental erionite exposure. Although the erionite fibre levels were low, proportions were high in airborne dust samples in the environment. Both epidemiological and in vivo and in vitro experimental studies have confirmed the high potency of erionite to induce mesothelioma [6-12]. Indeed, retrospective mortality studies have revealed mesothelioma to be the cause of death in 23–50% of those who had resided in the "erionite" villages [3, 6]. Malignant mesothelioma may arise as a familial disease in these villages. The high potency of erionite to induce mesothelioma is also pointed out by the fact that there were 58 patients referred to a tertiary care centre from the erionite villages whereas there were 77 from more than 30 villages environmentally exposed to asbestos in central Turkey in a recent analysis of 135 patients with pleural mesothelioma [3]. The median survival of pleural mesothelioma, patients associated with erionite exposure after diagnosis was significantly shorter than those associated with asbestos exposure (13.5±0.7 months versus 21.5±0.8 months, respectively) [3]. This difference may also add to the evidence of a high carcinogenic potency of erionite. In a recent study, flow cytometric deoxyribonucleic acid (DNA) analysis showed significantly higher percentages of aneuploidy in patients with erionite-induced mesothelioma compared to those with an asbestos aetiology (73% versus 17%) [13]. In fact, erionite is considered a more potent fibrous carcinogen than asbestos for mesothelioma. Although it may seem to be a local health problem for Turkey, mesothelioma cases due to erionite among those migrating from erionite villages have been published under the title of "imported mesothelioma" [14]. Another important aspect of the problem is that the potency of erionite to induce this malignant disease has drawn attention to the importance of the fibrous nature of both the minerals in the pathogenicity of mesothelioma.

Due to the early age at the onset of exposure, the mean ages of mesothelioma patients with environmental exposure to mineral fibres are much lower than those who are occupationally exposed to asbestos. The mean age of patients with mesothelioma due to previous occupational exposure to mesothelioma is ~60 yrs [1]. However, it is not a rare occurrence to have patients under the age of 40 yrs in our practice. Among 135 patients with pleural mesothelioma, 17 of 77 (22%) and 22 of 58 (38%) patients were <41 yrs of age with mean ages of 46.4±10.6 yrs and 49.7±11.7 yrs for the asbestos and erionite exposed patients, respectively [3]. The youngest patients were 26 and 27-yr old. Another difference from the occupational group may be that the sex difference for occurrence of the disease is much less significant in the environmentally exposed group. In fact, close follow-up of the villagers in the erionite-exposed group has revealed a similar number of cases among males and females. There may also be rare atypical presentations such as superior vena cava and Homer syndromes or fever of unknown origin [3]. Similar to the situation with asbestos, malignant peritoneal mesothelioma is less frequent than pleural mesothelioma among the patients.

Due to the difficulties in the pathological diagnosis of malignant mesothelioma even with histochemistry, we do not agree with the authors that cytology may be useful. In the previous series, ~40% of the patients were diagnosed either by closed pleural biopsy or thoracoscopy [3]. We agree that thoracoscopy is a very valuable procedure both for the diagnosis and staging of patients with a presumptive diagnosis of mesothelioma with no apparent morbidity or mortality.

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References


From the authors:
I was very interested by the letter of Z.T. Selçuk and colleagues. Their papers on environmental exposure to erionite initiated by Y.I. Baris are universally known. I completely agree with their observations. With regard to tremolite exposure, we have found a very similar situation in Corsica [1]. We all agree that thoracoscopy is better than fluid cytology and represents the gold standard for diagnosis and initial prognosis of mesothelioma.

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References

"Cross-talk" among a multiplicity of pro-inflammatory agents: main cause of tissue damage in pulmonary inflammation?

To the Editor:
I have recently read with much interest two excellent reports in the European Respiratory Journal which discussed the role of neutrophil proteinases and defensins in chronic obstructive pulmonary disease [1] and in airway diseases [2]. Reading through these articles, it was surprising not to find any considerations of a major aspect related to the elucidation of the possible mechanisms of tissue damage in the lungs during inflammation. I refer to extensive studies from several laboratories which had proposed that tissue damage in inflammatory and infectious processes may primarily be the result of a synergistic "cross talk" among a multiplicity of pro-inflammatory agents (a multi-component system) [3, 4].

A series of publications [5–14] have shown that a severe and rapid membrane injury (necrosis) could be initiated in mammalian cells by a synergism among subtoxic concentrations of three major groups of agonists. These included a) oxidants (H₂O₂, peroxy radical, oxidants generated by xanthine-xanthine-oxidase, NO, HOCI, OONO⁻), b) membrane-perforating agents (microbial haemolysins/phospholipases A₂ and C, lysophosphatidies, free fatty acids, cationic proteins, histone [9] and defensins [5], and c) highly cationic proteolytic enzymes, (elastase, cathepsin G) [3, 4, 12]. These synergistic cytotoxic effects can be further amplified by certain cytokines. Furthermore, combinations of oxidants and elastase have also been shown to synergize to cause severe lung damage in animal models [6–10]. It has also been proposed that a deleterious synergism among microbial and host-derived pro-inflammatory agonists may frequently contribute to tissue injury in many infectious and post-infection complications [3, 4]. A notable example is, sepsis and the "flesh-eating" syndrome caused by highly toxigenic and invasive bacteria.

Other studies had also shown that subtoxic amounts of the membrane-active xenobiotics, ethanol, methanol, n-butanol and the pesticide linden [13], could also synergize with subtoxic concentrations of peroxide, proteinases and cationic agents to amplify the damage to endothelial cells in culture. The results with the xenobiotics are of especial interest and concern to pulmonologists as these volatile agents may be inhaled and might then synergize with oxidants, proteinases and cationic proteins released either by accumulating neutrophils or by activated lung macrophages to cause damage to both epithelial and endothelial cells.

It has also been documented that β-lactam antibiotics and a large variety of cationic agents including, elastase, cathepsin G, defensins, lysozyme, myeloperoxidase, spermere, spermordine, histones, polymyxin B and chlorhexidine are all capable of activating the autolytic wall enzymes (muramidases) in bacteria leading to bacteriolsysis [14]. Bacteriolsysis at least in Gram-positive bacteria induced either by β-lactams or by cationic agents can, however, be strongly inhibited by sulphated polyanions presumably by inactivating the autolytic wall enzymes responsible for breaking down the rigid cell wall. It is accepted that the massive release widely of bacterial wall components (lipopolysaccharide, lipoteichoic acid, peptidoglycan), in vivo, can activate macrophages to release cytotoxic cytokines, NO and also to activate the complement and coagulation cascades leading to sepsis, systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS) and multiple organ failure (MOF) [15].

Today there are controversial opinions and hot debates regarding the approaches to treat sepsis, adult respiratory distress syndrome (ARDS) and additional post-infectious and inflammatory sequelae [15]. Unfortunately, the exclusive use of single antagonists to treat these syndromes has yielded poor results. Such failures may principally be due to, a) the lack of adequate and rapid tests to predict the onset of such complications so that treatment of patients usually starts too late, and b) a lack of sufficient awareness that fighting the deleterious effects caused by synergistic cytotoxic mechanisms necessitates the use not of single antagonists but of cocktails comprised of a multiplicity of anti-inflammatory agents. Hopefully, a wider recognition of synergism concept of cellular injury [3, 4, 11–13] might offer a new and more realistic approach to this complex and still unsolved clinical problem.

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Sarcoidosis and cancer revisited

To the Editor:

The authors of a recent article in the European Respiratory Journal [1] have chosen, by identical means, to verify the hypotheses of Brüncker and Wibeck [2] that: a) sarcoidosis and malignancy are associated; b) sarcoidosis predisposes to malignancy; c) this pattern is encountered predominantly in patients with chronic sarcoidosis; and d) the association is limited to lung cancer and lymphomas. This study has disposed of the third part of the hypothesis, the late age of onset of sarcoidosis in association with malignancy is, as the authors point out, an artefact of the study design, which confines itself to a limited (as opposed to a lifetime) period of observation.

If one pools the author’s male and female data, one finds an odds ratio (OR) observed/expected (O/E) of 1.25, 95% confidence interval (CI) = 0.8, 1.9; if one conforms to the practice of previous studies and excludes nonmelanoma skin cancer, the OR is 1.16, 95% CI = 0.7, 1.8. Does this resolve this vexatious dispute? Not quite. Absence of evidence is not evidence of absence.

For a two-tailed α of 0.05, this study provides a β error of 85%, i.e., an 85% likelihood of incorrectly accepting the null hypothesis if there is a 25% higher incidence of malignancy in patients with sarcoidosis; a sarcoidosis sample size of 4,500, nearly 10-fold that available to the authors, would be required to reduce the β error to 20%; if one excludes nonmelanoma skin cancers the required sample size would be correspondingly larger. The epidemiological approach is even more problematic for specific malignancies: to achieve a 90% power at the same α level, 1,500 patients with sarcoidosis, followed for 10 yrs would be required to demonstrate an association between sarcoidosis and Hodgkin’s disease if the true frequency of Hodgkin’s disease in persons with sarcoidosis was 10-times that in the general population. In brief, the demonstration of an association between sarcoidosis and malignancy by epidemiological means requires unattainable sample sizes, which is why we proposed linkage criteria [3].

By excluding patients with pre-existent or coincidental cancer, the authors limited their hypothesis testing to whether sarcoidosis engenders the development of malignancy. Several authors have suggested the opposite: that malignancy and/or therapy infrequently generate a systemic granulomatous response not easily distinguished from sarcoidosis [3–5]. Can the authors provide any information on this hypothesis from their database?

The authors point out that we observed about half as many cases of sarcoidosis associated with malignancy as they did, 4.5% versus 8.6% [3]. The studies are not comparable however, because we did not exclude persons with pre- or co-existent cancer and the duration of observation was considerably more brief.

I was curious to know why the authors excluded persons with bilateral hilar adenopathy had sarcoidosis [6]. Could this exclusion have skewed the data?

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If one pools the author’s male and female data, one finds an odds ratio (OR) observed/expected (O/E) of 1.25, 95% confidence interval (CI) = 0.8, 1.9; if one conforms to the practice of previous studies and excludes nonmelanoma skin cancer, the OR is 1.16, 95% CI = 0.7, 1.8. Does this resolve this vexatious dispute? Not quite. Absence of evidence is not evidence of absence.

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References
From the authors:

We thank J.M. Reich for his commentary on our study on malignancy in sarcoidosis, and for the opportunity to reply to the letter. J.M. Reich states that "absence of evidence is not evidence of absence". Of course we cannot disagree, but we are still convinced that our conclusions are valid. Our purpose was to examine the occurrence of malignancy in a sarcoidosis population, with the inherent weaknesses of such a study, as also discussed in our article [1]. The question of an overall association of sarcoidosis and malignancy including whether malignancy predisposes to sarcoidosis was beyond the scope of the study. Three of our patients had malignant disease diagnosed before sarcoidosis; they were excluded from the calculations. Therefore, our study could not provide any information on the occurrence of systemic granulomatous response to malignancy or cancer therapy. We also agree that the question is difficult to solve using ordinary epidemiological methods. Therefore, Reich et al. [2] used a "linkage analysis" in their study on overall association of malignancy and sarcoidosis. However, this methods also has several drawbacks as pointed out in a later discussion [3]. Therefore it may also be inappropriate to compare our results with those of Reich et al. [2].

Although our sample size was rather small for epidemiological studies, it is noteworthy that our results are in agreement with a similar Danish study from the Copenhagen area [4], and in both studies rather long observation periods were available, proving the validity of the results. So, although malignancy may theoretically be more frequent than expected in sarcoidosis, this figure is in reality extremely small for practical reasons.

Regarding Reich’s remarks on bilateral hilar adenopathy and our demand for an observation period of at least 6 months before inclusion in the series, it should be stated that a sufficient period of observation was most important in asymptomatic patients without histological evidence. If granulomas were demonstrated the patient was included at once. Since the 1960's it has been found that isolated bilateral hilar adenopathy in asymptomatic patients in the majority of cases was caused by sarcoidosis, as later confirmed by Winterbauer et al. [5] and more recently by Reich et al. [6].

The requirement of 6 months of observation (with frequently repeated examinations) was used to avoid inclusion of cases with other causes of bilateral hilar adenopathy or, when bilateral hilar adenopathy was slight or doubtful, to exclude the patient if bilateral hilar adenopathy in subsequent examinations could not be confirmed. Actually we have no exact number of these patients, but in fact they were rather few and we do not think that their exclusion significantly skews the data.

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References