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Drug-induced eosinophilic pleural effusion

To the Editors:

We read with great interest the article by ALAGHA *et al.* [1] in the June issue of the *European Respiratory Review*. Since, in our opinion, eosinophilic pleural effusion (EPE), and drug-induced EPE in particular, is an interesting issue, we would like to add some comments to this article.

It should be realised that our knowledge on drug-induced EPE comes almost exclusively from case reports. Although none of the larger series presenting the aetiology of EPE reported the true incidence of drug-induced EPE, the percentage of patients with drug-induced EPE seems to be low. Nevertheless, as in the majority of these patients drug discontinuation is sufficient for resolution of pleural effusion, pharmacological agents should always be considered as a potential cause of pleural effusion, particularly in EPE.

Although numerous drugs can induce pleuritis and pleural effusion, the list of agents associated with eosinophilic pleuritis is not extensive [2–4]. Some drugs used in psychiatry and neurology are some of the most important, including valproic acid (and its derivatives) and dantrolene [5–8]. EPE was also reported as a complication of treatment with tazinidine, trimipramine and fluoxetine [9–11]. It is interesting that, in a substantial number of reports on drug-induced EPE, two or more drugs that can potentially induce pleural effusion were used. This was the case in the first patient described by ALAGHA *et al.* [1], who was treated with dantrolene and fluoxetine. Similarly, two patients with EPE related to valproic acid and sodium valproate, respectively, were also treated with clozapine [12, 13]. Interestingly, when valproic acid and clozapine are used together, clozapine might be a true cause of pleural effusion as demonstrated by DALY *et al.* [14]. Clozapine-induced pleuritis was reported in one patient who was concomitantly treated with olanzapine [15]. These examples show the crucial

role of thorough clinical evaluation, including drug withdrawal and re-challenge in making a causative diagnosis of drug-induced pleural effusion.

In order to list the most important drugs associated with EPE, two other groups should also be presented. The first is quite inhomogeneous and includes drugs mainly used in cardiology and internal medicine, these are: warfarin, diltiazem, simvastatin, imidapril, propylthiouracyl and mesalamine. The second group includes the following chemotherapeutics and antibiotics: nitrofurantoin, daptomycin and tosufloxacin. A comprehensive review on drug-induced pleural effusion was published in 2004 [16].

There is one general statement regarding EPE in the report by ALAGHA *et al.* [1] which, in our opinion, requires correction and comment. Citing an article by ADELMAN *et al.* [17], the authors state that a specific cause of EPE could be identified in only 25% of patients [1]. We would like to emphasise that, although the paper by ADELMAN *et al.* [17] has long been one of the most important sources of our knowledge on epidemiology of EPE, it was based on analysis of 23 papers published between 1955 and 1982. Thus, the data from that study are quite old. However, even in this paper the cause of EPE could be identified in 65% of patients and only 35% of cases were classified as “idiopathic” EPE [17]. Recently, some relevant articles on EPE epidemiology have been published. Our analysis of the largest, single-centre treated group of patients with EPE showed that a causative diagnosis was not established in only 14.1% of these patients [18]. A similar result (15.6% idiopathic EPEs) was reported by MARTINEZ-GARCIA *et al.* [19]. It should also be noted that other authors reported a higher percentage of patients with EPE of unknown origin. This percentage, however, did not exceed 30–32% [2, 20]. A lower number of patients with unknown cause of EPE in the recent studies might be related to the advances in the diagnosis of pleural effusion, but also to changing aetiology of EPE. This was elegantly demonstrated in a paper recently

published by OBA and ABU-SALAH [21]. While malignancies were responsible for only 8% of all EPEs reported by ADELMAN *et al.* [17], they accounted for 111 (30%) out of 369 EPE cases reported in the six studies published in the past decade [21]. Cumulative prevalence of malignancies in patients with EPE reported in 17 studies published between 1967 and 2009 has increased from 7% to 25% [21]. In our large series, malignancies were the most common cause of EPE, responsible for 35% of EPE cases [18].

Some clinical and laboratory data might help to roughly predict the probability of various aetiologies of EPE. Analysis of different studies shows that the epidemiology of EPE might be closely related to the local epidemiological setting. The percentage of tuberculous effusion in EPEs developing in populations with a high prevalence of tuberculosis was as high as 10–39.6% [20, 22], while it was only 0–2% in the setting of low or intermediate tuberculosis prevalence [2, 18, 23]. In our previous study, an interesting relationship was found between the percentage of eosinophils and EPE aetiology. The percentage of patients with malignant EPE was inversely related to the percentage of eosinophils in pleural effusion. An opposite relationship was found for patients with pleural effusion of unknown origin [18]. A similar relationship between the probability of malignancy and eosinophil percentage was also demonstrated in a recent meta-analysis [21]. The two cases reported by ALAGHA *et al.* [1] seem to be consistent with the relationship presented above. The percentage of pleural fluid eosinophils was high (55 and 75%, respectively) and both described patients had a non-malignant aetiology of EPE [1].

To summarise, we believe drug reactions should be considered as a potential cause of pleural fluid accumulation in all patients with EPE. However, drug-induced EPE should be considered on a broad basis of EPE aetiology. Since a specific cause of EPE can be identified in the majority of cases, all patients with this type of pleural effusion require rigorous and full diagnostic algorithm.

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