**Supplementary data**

**Table S1: Other concomitant therapies**

|  |  |  |
| --- | --- | --- |
| **Case** | **Treatment\*** | **Type of drug induced respiratory disease reported in Pneumotox®** (www.pneumotox.com) |
| Case 1 | Omeprazole  Domperidone | Angioedema and urticaria, cough |
| Case 2 | Ondansetron  Tramadol  Fondaparinux | Hypoventilation, respiratory acidosis, multiple organ dysfunction |
| Case 3 | Loperamide  Tinzaparine  Metoclopramine |  |
| Case 4 | Irbesartan  Furosemide  Atenolol  Nadroparine calcique  Domperidone  Tramadol-Paracetamol | Hypoventilation, respiratory acidosis, multiple organ dysfunction |
| Case 5 | Prednisone  Venlafaxine  Divalproate de sodium  Alprazolam  Zolpidem | Subacute pneumonitis/ILD, eosinophilic pneumonia, bronchospasm  Pulmonary edema |
| Case 6 | Prednisone  Sulfate de morphine  Rabeprazole  Furosemide  Tinzaparine  [Amitriptyline chlorhydrate](http://www.vidal.fr/substances/6678/amitriptyline/) | Diffuse alveolar damage, pulmonary edema, ARDS, diffuse alveolar hemorrhage, bronchospasm  Eosinophilic pneumonia, ARDS, hypoventilation |

\*We could not exclude an interaction between drugs; however none of these treatments was stopped, except crizotinib

**Table S2: Criteria for assessing crizotinib associated ILD**

|  |  |  |
| --- | --- | --- |
| **Intrinsic criteria from the clinical analysis** | | |
| Exposition to Crizotinib | All cases | |
| Beginning of symptoms after crizotinib instauration | All cases | |
| No ILD before Crizotinib | Except for Case #6 who developed ILD after erlotinib exposition  No thoracic radiotherapy | |
| Compatible presentation | Case #6: ARDS  Index Case and Cases 2 to 5  *• Clinical:* few symptoms, cough, dyspnea  *• Radiologic:* GGO lesions far from tumoral lesions, in normal lung, and tended to migrate over time. These lesions were not extensive or diffuse, but rather localized  *• BAL:* T-lymphocytic alveolitis with a predominant CD4 cell subset.  *• Histology:* no specific lesion, no tumor cell | |
| Exclusion of others etiologies | Medications | See Table IV |
| Environmental exposure | No changes in environmental exposure or lifestyle reported by cases at this time in comparison to usual  Negative results for serologies for domestic exposure hypersensitivity pneumonitis |
| Auto-immunity | Negative results of : antinuclear antibody, anti-DNA antibody, antineutrophil cytoplasmic antibody, C3 and C4 complement components, rheumatoid factor, anti-cyclic citrullinated peptide antibody, anti-aminoacyl-tRNA-synthetase antibody including PL1, 7, and 12: negative (except Case #2) |
| Infection | Extensive microbiologic evaluations (sputum, blood cultures, bronchial aspiration, BAL) proved negative for virus, bacteria, acid-fast bacilli, fungi, and parasites  Negative serology test results for atypical pathogens |
| Cardiovascular disease | Echocardiography: normal systolic function. Normal brain natriuretic peptide dosage  No intra-alveolar haemorrhage in BAL |
| Lung cancer progression | Absence of tumor cells in BAL nor adenocarcinoma in bronchial and tranbronchial biopsies  FDG-PET: partial tumour response |
| Improvement by stopping crizotinib | Regression of ILD for all cases except Case #6 | |
| Relapse with reintroduction of crizotinib | Three cases with recurrence | |
| **Extrinsic criteria from the literature** | | |
| Other cases in systematic review of the literature | 9 cases described, 4 conducted to death, 4 with reintroduction of crizotinib, 1 relapse | |