Gastroesophageal Reflux Disease Is a Risk Factor for Severity of Organizing Pneumonia

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Key Words

Organizing pneumonia · Pyrosis · Gastroesophageal reflux · Relapse

Abstract

Background: The link between organizing pneumonia (OP) and gastroesophageal reflux disease (GERD) is not well known. There is little evidence in the literature to establish a causal link between GERD and OP. **Objectives:** The aim of the study was to assess the hypothesis that OP is more severe when it is associated with GERD and that it leads to more frequent relapses. **Methods:** In a retrospective study on 44 patients suffering from OP, we compared the clinical, radiological and histological characteristics of 2 groups, 1 composed of patients with GERD (n = 20) and the other of patients without GERD (n = 24). **Results:** The GERD group was distinguished by a higher number of patients with migratory alveolar opacities on chest radiography and thoracic computerized tomography (14/20 vs. 9/24; p = 0.03 and 18/20 vs. 13/24; p = 0.01), greater hypoxemia [60 (42–80) vs. 70 (51–112) mm Hg; p = 0.03], greater bronchoalveolar lavage cellularity [0.255 (0.1–1.8) vs. 0.150 (0.05–0.4) g/l; p = 0.035] and more frequent relapses (14/20 vs. 9/24; p = 0.03).

Conclusions: OP associated with GERD is more severe and results in more frequent relapses. Microinhalation of gastric secretions might induce lung inflammation leading to OP and relapse. We suggest that typical symptoms of GERD such as pyrosis should be investigated in OP.

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Introduction

Organizing pneumonia (OP) is a rare lung disease, the diagnosis of which is based on a range of radiological, anatomical and clinical evidence, as it includes a number of nonspecific signs that are common in lung diseases [1–4]. OP can have many causes: infection, radiation therapy, drugs, allogenic bone marrow graft or lung transplantation, inhalation of respiratory irritants as well as being secondary to systemic diseases (e.g. Sjögren's syndrome), hemopathy or solid tumors [1, 6–12]. When no cause can be determined, it is called cryptogenic organizing pneumonia (COP) [8, 13].

Gastroesophageal reflux disease (GERD) is a common disease in the general population (prevalence: 20–30%) [14–16]. Pyrosis is the typical symptom of GERD (there

are other less specific symptoms such as regurgitation, stomach pain, dysphagia, hiccup, cough, posterior laryngitis and dental erosion) [17, 18]. GERD is known to be associated with many lung conditions [16, 19–24]. Some authors have suggested that GERD could trigger OP [1, 25–27]. However, there is little evidence in the literature to establish a causal link between GERD and OP [1, 25, 28, 29].

The aim of this study was to assess the hypothesis drawn from our clinical practice that OP associated with GERD is distinguished by its severity and by a greater risk of relapse. To this end, we compared 2 groups: 1 composed of patients with GERD when OP occurred (GERD+) and the other of patients with no reported GERD (GERD–).

Patients and Methods

Criteria for Selecting Cases and for Validating the Diagnosis of OP

Cases were retrospectively identified from the medical procedure reference codes of patients who were admitted and seen in the Respiratory Diseases Department of the University Hospital of Tours between 1995 and 2012. OP cases were selected by identifying and analyzing 136 files. The relevance of the OP diagnosis was reevaluated a posteriori. Cases were retained when the pathologist concluded that there were ‘connective endoalveolar buds’ (e.g. aggregates of fibroblasts and immature collagen matrix within the terminal airspaces) [30] in the absence of other abnormalities. The diagnosis was not considered if other specific histological patterns were observed, notably those suggesting nonspecific interstitial pneumonia or other interstitial disease, diffuse alveolar damage (hyaline membranes), Wegener’s granulomatosis, hypersensitivity pneumonitis, neoplasia and infection [1, 30–32].

When biopsy could not be performed, cases were retained if the following clinical and radiological criteria were met:

- Clinical – the association of ≥ 2 of the following symptoms: fever $>37.5^{\circ}\text{C}$, cough or dyspnea associated with unilateral or bilateral crackles. The evolution of the symptoms had to include one or more of the following criteria: failure to respond to antibiotics, a good response to corticosteroids, clinical relapse and spontaneous recovery [33–35].
- Imaging – alveolar opacities [from ground-glass to consolidation on thoracic computerized tomography (CT)], preferentially inferior and peripheral, single or multiple and migratory. Evolutive imaging features had to include one or more of the following criteria: a good response to corticosteroids, relapse and possible spontaneous recovery [36].

An infection was ruled out in all cases by microbiological analysis and all patients received more than one line of antibiotics without remission of the OP.

Following the analysis of the 136 files, 56 cases of OP were retained (fig. 1). The remaining 80 cases were other infiltrative lung diseases. Twelve of 56 cases were discarded due to a lack of data (e.g. no detailed record of initial clinical, biological or imaging examination or information regarding GERD symptoms). Information regarding the presence or absence of GERD symptoms could

Fig. 1. Selection of cases and distribution of the two groups (GERD+ and GERD–). BO = Bronchiolitis obliterans; ILD = interstitial lung diseases; OP = organizing pneumonia; GERD+ = patients with gastroesophageal reflux disease (n = 20); GERD– = patients without gastroesophageal reflux symptoms (n = 24).

be found in the charts of the 44 retained cases. Histological confirmation of OP was established in 16 of 44 patients (4 in the GERD+ group and 12 in the GERD– group), 1 by transbronchial biopsy and 15 by surgical biopsy. The patients who did not undergo surgical biopsy were considered to be too severe to tolerate the surgery.

French legislation does not require ethics committee approval or the informed consent of patients for retrospective data collection that conforms to medical current practice. The database was anonymous and complied with the restrictive requirements of the ‘Commission Nationale de l’Informatique et des Libertés’, the committee that ensures the application of data privacy laws in France.

Characteristics of the Patients

Clinical parameters were collected for each patient: sex, age at diagnosis, previous medical history, exposure to respiratory irritants, smoking, pyrosis, previous treatment, treatment by proton pump inhibitors (PPI), the clinical features of OP, the laterality of the disorder, antibiotic therapy, corticosteroid therapy, relapses and signs of systemic disease. Lung function tests, arterial blood gas and biological data (biochemistry, hematology, immunology and microbiology) were collected. Endoscopic data [bronchial fibroscopy, bronchoalveolar lavage (BAL), esogastroduodenal endoscopy (EGDE) and other GERD tests (pH-metry, manometry)] and radiological data (thoracic radiography and thoracic CT for detection of migratory alveolar opacities) were also collected. To define the migratory character of the opacity, we compared each patient’s thoracic CT and radiography at diagnosis with reevaluations performed 3 months later. The two radiological exams used to define the migratory character of the opacities were made prior to the corticosteroid treatments. The migratory character of the opacities was defined by differences in ≥ 1 opacity, not located in the same lobe, between the two radiological exams. Relapses were

Table 1. Characteristics of patients in GERD+ and GERD– groups

	GERD+ group (n = 20)	GERD– group (n = 24)	p
Age, years	71 (32–88)	61 (34–82)	0.1
Male	12	13	0.69
Smoker or former smoker	10	12	1
Exposure to respiratory irritants	6	3	0.26
Radiotherapy	2	2	1
COP	11	15	0.6
Number of patients who had arterial blood gas	13	14	0.6
PaO ₂ , mm Hg	60 (42–80)	70 (51–112)	0.03*
OP of the right lung only	1	3	0.6
Bilateral OP	19	20	0.35
Diagnostic delay, months	2 (0.5–60)	2 (1–120)	0.88
PPI use	10	3	0.009*
Migratory alveolar opacities on chest X-ray	14	9	0.03*
Migratory alveolar opacities on CT	18	13	0.01*
Hiatal hernia on CT	7	4	0.16
Distension of the esophagus on CT	4	4	0.77
Lung function testing performed	18	22	1
VC, % of expected value	97 (57–143)	82 (33–125)	0.07
FEV, % of expected value	95 (57–140)	80 (28–118)	0.14
FEV/FVC ratio (<70%)	4	5	0.94
TLC, % of expected value	91 (62–105)	80.5 (54–110)	0.21
DLCO/VA ratio, % of expected value	96 (57–143)	87 (59–156)	0.84
Bronchial fibroscopy performed	12	15	0.85
BAL cellularity, G/L	0.255 (0.1–1.8)	0.150 (0.05–0.4)	0.035*
Macrophages, % of BAL	54.5 (10–87)	63 (2–95)	0.31
Neutrophils, % of BAL	14 (3–56)	6 (1–96)	0.21
Lymphocytes, % of BAL	16 (1–85)	10 (2–75)	0.29
Eosinophils, % of BAL	0 (0–29)	0 (0–14)	0.83
Blood eosinophilia, G/L	0.13 (0–0.78)	0.17 (0–0.79)	1
C-reactive protein, mg/l	121 (5–262)	145 (20–323)	0.76

Figures denote number or a median value (minimum–maximum). * $p < 0.05$.

defined as the reappearance of a radiological pattern consistent with OP, with compatible clinical features and no other identified cause, after a complete remission of the disease (with or without corticosteroids). Finally, histological data were collected when a biopsy had been performed. Hiatal hernia on chest radiography was defined by a retrocardiac gas-filled structure. Identification of gastric rugal folds, soft-tissue fullness separate from the tubular esophagus or a lobulated or irregular enteral contour above the esophageal hiatus was necessary to diagnose hiatal hernia on thoracic CT [37].

Gastroesophageal Reflux Disease

Medical charts in our department always include clinical questionnaires related to the presence or absence of GERD symptoms. In all 44 retained cases, patients had been asked about the presence or absence of GERD symptoms and, in particular, if they had ever experienced pyrosis. Our patients were divided into 2 groups (fig. 1; table 1). The diagnosis of GERD (GERD+ group, $n = 20$) was made if typical pyrosis existed, associated with the response to

PPI treatment. Diagnosis had been validated further for 13 patients in this group [hiatal hernia or esophagitis on EGDE, acid reflux revealed by 24-hour pH-metry (pH <4 lasting longer than 10 s for >5% of the time) and hypotonic lower esophageal sphincter revealed by esophageal manometry] [38]. Pyrosis had been experienced before the beginning of the disease by all the patients in the GERD+ group. In the GERD– group, patients had never presented with pyrosis or other typical symptoms of GERD ($n = 24$). In this group, 2 patients underwent investigations ruling out GERD (EGDE and pH-metry were normal for 1 patient and EGDE and manometry for another).

Statistical Analysis

All data were expressed as the median. The χ^2 test or the Fisher exact test was used to compare categorical data for the GERD+ and GERD– groups. For the quantitative data, the Mann-Whitney test was conducted. Statistical analysis was performed using Graphpad Prism v5.0 (Graphpad Software, La Jolla, Calif., USA). A p value <0.05 was considered statistically significant.

Table 2. Treatment and relapses of OP in the GERD+ and GERD– groups

	GERD+ group (n = 20)	GERD– group (n = 24)	p
Corticosteroid therapy	17	18	0.41
Total dose of corticosteroid therapy (prednisone equivalent), mg	3,800 (700–5,500)	3,750 (2,300–4,600)	0.26
Relapse	14	9	0.03*
Relapse time delay, months	6 (1–24)	4 (2–12)	0.91
Diagnostic delay >4 months	5	5	0.74
Time between the start of corticosteroid therapy and recovery, months	1.5 (0.25–6)	1.25 (0.5–4)	0.81
Duration of corticosteroid therapy, months	4 (2–6)	4 (2–6)	0.77
Higher level of liver enzymes	2	2	1
Severe hypoxemia (PaO ₂ <55 mm Hg)	6	5	0.48
Multifocal opacity on CT	20	21	0.24
Lung biopsy performed	4	12	0.11
Collagen fibrosis on histology	1	3	1

Figures denote number or a median value (minimum–maximum). None of the predictive factors described in the literature were found to be significantly relevant to the OP relapse.

* p < 0.05.

Results

The characteristics of the 2 groups are summarized in tables 1 and 2. The GERD+ group (n = 20) was not significantly different from the GERD– group (n = 24) in terms of age, sex and smoking status.

Ten patients in the GERD+ group were under PPI compared to 3 in the GERD– group. In the GERD– group, PPI had been initiated in 1 patient who was on a nonsteroidal anti-inflammatory treatment for articular pain due to rheumatoid arthritis, in another because of a high level of urea during dialysis and in a third patient due to a history of gastric ulcer and the initiation of aspirin for myocardial infarction. None of these 3 patients presented other clinical evidence of GERD (table 1).

Characteristics at OP Diagnosis

No significant difference in the clinical characteristics of OP was found between groups (table 1). No difference was found regarding diagnostic delay of the OP, dyspnea, fever, pulmonary auscultation or respiratory rate (data not shown). There were no significant differences between groups with regard to exposure to respiratory irritants (GERD+: n = 6, GERD–: n = 3), previous radiotherapy (GERD+: n = 2, GERD–: n = 2) or the identification of a cause of OP (GERD+: n = 9 secondary OP; GERD–: n = 9 secondary OP). See the Methods section and online supplementary figure 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000369470).

Upon diagnosis of OP, arterial blood gas revealed that the PaO₂ of patients breathing ambient air was lower in the GERD+ group (n = 13) than in the GERD– group (n = 14) [60 (42–80) vs. 70 (51–112) mm Hg; p = 0.03; fig. 2]. One patient who presented with severe OP with acute respiratory failure and requiring a high dose of oxygen was in the GERD+ group. However, there was no difference between the 2 groups in terms of the need for oxygen (data not shown). There was no difference between the 2 groups regarding eosinophilia, C-reactive protein or respiratory function at diagnosis or after OP was cured (table 1).

We compared the COP (n = 26) and the secondary OP (n = 18) groups (see e-table 1 in the online data supplement). There was no difference between these 2 groups except for the PaO₂ value. PaO₂ was lower in the secondary OP group (in 13/18 patients) than in the COP group (in 14/26 patients), i.e. 52 (43–72) versus 70 (42–112) mm Hg (p = 0.008).

The migratory character of the opacity was more frequent in the GERD+ group than in the GERD– group (radiological presentation: 14/20 vs. 9/24; p = 0.03; thoracic CT appearance: 18/20 vs. 13/24; p = 0.01). Patients were comparable regarding other radiological and CT characteristics. In both groups, OP was bilateral.

Hiatal hernia was not visible on chest radiography in any patient, and was not significantly more visible on thoracic CT in the GERD+ group (7/20 vs. 4/24; p = 0.16).

Fig. 2. PaO₂ in ambient air in mm Hg in GERD+ and GERD- groups (results are presented as median and interquartile range), $p = 0.03^*$, $* p < 0.05$.

Fig. 3. BAL cellularity in G/L in GERD+ and GERD- groups (results are presented as median and interquartile range), $p = 0.035^*$, $* p < 0.05$.

Fig. 4. Left: High-power photomicrograph showing foreign material consistent with food (solid arrows) (Hemalun eosin safran, original magnification $\times 200$). Right: High-power photomicrograph showing foreign material consistent with food (solid arrow) (Hemalun eosin safran, original magnification $\times 400$).

BAL cellularity was significantly higher in the GERD+ group ($n = 12$) than in the GERD- group ($n = 15$), i.e. 0.255 (0.1–1.8) vs. 0.150 (0.05–0.4) g/l ($p = 0.035$; fig. 3). The alveolar lavage formula (cell count and differential: alveolar macrophages, neutrophils, eosinophilia, lymphocytosis and erythrocytes) did not differ between the 2 groups. Food was found in bronchial aspiration of 1 patient in the GERD+ group (fig. 4). The pathology analysis showed endoalveolar buds of granulation tissue in all samples ($n = 16$) and collagen fibrosis in 4 samples. There was no significant difference regarding collagen fibrosis (1/4 GERD+ patients vs. 3/12 GERD- patients).

Treatment and Relapse of OP

The patients in the 2 groups were not treated differently (table 2). There was no significant difference regarding the use of corticosteroids, their effectiveness or the onset of their action. The cumulative dose of corticosteroids did not differ between the GERD+ group [3,800 mg prednisone equivalent (700–5,500 mg)] and the GERD- group [3,750 mg prednisone equivalent (2,300–4,600 mg)], and the mean duration of treatment was similar in the 2 groups (3.9 vs. 4 months; $p = 0.77$). There were no significant differences regarding the number or duration of hospitalizations (data not shown). None of the 44 patients had been prescribed PPI following the diagnosis of OP.

Relapses after the OP were significantly more frequent in the GERD+ group (14/20) than in the GERD- group (9/24) ($p = 0.03$; table 2). The mean time to relapse was comparable in the 2 groups, i.e. 6.5 months for GERD+ and 5.3 months for GERD- ($p = 0.91$; table 2). The 10 patients in the GERD+ group who were treated with PPI did not have fewer relapses than those who did not receive PPI (6/10 relapses in the PPI+ group vs. 8/10 in the PPI- group; $p = 0.6$). No PPI treatments were initiated during the treatment of OP. If a PPI had already been prescribed, it was not stopped.

Discussion

This study of 44 cases of OP confirms our hypothesis that OP associated with GERD can be distinguished on the basis of criteria that overall affect severity: a more frequent migratory character of opacities on chest radiography and thoracic CT, hypoxemia and significantly more marked BAL cellularity as well as significantly more relapses.

The differences observed between the GERD+ and GERD- groups suggest the possible role of GERD in the spread and persistence of the inflammatory reaction of the lung. For example, the fact that the number of patients with migratory opacities was higher in the GERD+ group could be linked to the effect of positional variations during sleep and to their consequences on the extension of the chemical aggression of the bronchial epithelium and alveoli by gastric acid secretions. The role of the patient's sleeping position in the topography of the lung lesions has previously been described in a GERD patient: Barnes et al. [29] found unilateral OP lesions in a patient who preferred sleeping on the affected side. This has also been suggested in idiopathic pulmonary fibrosis [39, 40].

The significantly more marked hypoxemia in patients with GERD is consistent with a greater severity of the OP. The significantly higher BAL hypercellularity in the GERD+ group also supports the hypothesis of a particularly marked inflammatory reaction to the acid aggression of the bronchial epithelium by gastric secretions, although no evidence of a link between BAL cellularity and lung disease severity has ever been reported. In a case report describing OP secondary to a hiatal hernia, cellularity was also very high (0.850 g/l) [27].

GERD is probably not the sole reason explaining a lower PaO_2 . In the secondary OP group, PaO_2 was also lower and there was no other difference with the COP group, in particular regarding the number of patients

with pyrosis or the number of relapses. The etiology of OP was not a confounding factor. It is known that secondary OP can have a more severe prognostic. Lohr et al. [41] compared COP and secondary OP and did not find more relapses or a lower PaO_2 , but the 5-year survival was lower in the secondary OP patients and respiratory-related deaths were more frequent.

Our study also found that relapses were more frequent in the GERD+ group. Relapse is one of the clinical characteristics of OP. However, there have been very few studies on the precipitating factors [42–45], and to the best of our knowledge, the hypothesis of a possible link with GERD has never been raised. Relapses in our study were defined as previously in the literature [42, 43, 45]. In a study of 18 cases of OP, Watanabe et al. [42] found that the PaO_2 of relapsing patients (55 mm Hg) was significantly lower than that of patients with no relapse (78 mm Hg). In our series, the patients in the GERD+ group had a lower PaO_2 at diagnosis than those in the GERD- group. However, the mean PaO_2 was not significantly different between the 23 relapsing patients (66 mm Hg) and the 21 patients without relapse (60 mm Hg) ($p = 0.7$; online suppl. table 2). The patient in the GERD+ group who initially presented with acute respiratory failure had a relapse 3 months after remission. Lazor et al. [43] studied the characteristics of relapses of COP in 48 patients. They revealed the role of cytolysis and cholestasis, and found that delay in diagnosis and in initiating corticosteroid treatment was more common in the relapsing patients. These findings were not observed in our study or by Watanabe et al. [42]. In a study on 6 patients presenting with COP, Perrin et al. [44] found that collagen fibrosis in the interstitium was significantly more apparent in relapsing patients. In our study, the patients in the 2 groups who had undergone pathological examination did not show significant differences with regard to collagen fibrosis. Lastly, Barroso et al. [45] carried out a 19-year retrospective study of 33 cases of COP. They found that relapse was more common in cases with low levels of liver enzymes and with multifocal opacities, and that there was a tendency to relapse in cases with shorter corticosteroid treatment and rapid radiological recovery. In our study, there was no difference between the 2 groups in the duration of corticosteroid treatment or in the multifocal character of the lesions on imaging.

In our study, PPI did not seem to prevent relapse in the GERD+ group. However, few patients (10/20) were treated for their symptoms. In France, GERD guidelines state that PPI should be prescribed only if pyrosis occurs more than once a week. PPI treatment seemed to be effective in

only 6/10 patients (i.e. only 6 patients described the absence of pyrosis while the other 4 were still symptomatic). There were fewer relapses (2/6) among the patients who responded to PPI than among the rest of the patients together, i.e. 10 patients who did not receive PPI and 4 patients whose symptoms persisted despite PPI (12/14 relapses; $p = 0.037$). Patients characterized as PPI responders were not different from the other patients in term of symptoms and PaO_2 (60 vs. 55.5 mm Hg; $p = 0.8$).

The limitations of our study are linked to its retrospective character. Although all 44 patients were clinically screened for pyrosis, the diagnosis of GERD was documented by complementary investigations in only 13 of the 20 patients in the GERD+ group. Typical symptoms of GERD might be absent in some respiratory diseases, such as idiopathic pulmonary fibrosis. However, in cases presenting with typical pyrosis, the clinical diagnosis is currently considered sufficient to initiate PPI treatment [14, 15, 38, 46–48]. In the GERD– group, none of the patients had nontypical GERD symptoms (data not shown). Our study did not aim to examine these issues, but it is noteworthy that the prevalence of GERD in our sample (45%) was greater than in the general population, where it has been found to be 30% at the most [24, 38]. Three patients in the GERD– group received PPI treatment.

GERD had been clinically ruled out very thoroughly, and it was clear that PPI had not been prescribed because of suspected GERD.

Conclusion

OP associated with pyrosis is characterized by a higher number of patients with migratory radiological opacities, lower PaO_2 on admission, higher BAL cellularity and a greater risk of relapse. We hypothesize that GERD can cause repeated microinhalations of gastric acid secretions, contributing to the maintenance of bronchial and alveolar inflammation, which could lead to OP itself and also to relapses. Data suggest that GERD may be a risk factor for OP and should be investigated prospectively before making recommendations for management and treatment. We suggest that typical symptoms of GERD such as pyrosis should be investigated in cases of OP and especially in the event of OP relapse.

Financial Disclosure and Conflicts of Interest

There is no conflict of interest.

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