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Pulmonary pathology in patients with ulcerative colitis treated with mesalazine — a challenging and complex diagnostic problem. Case series and literature review

Choroba płuc u pacjentów z wrzodziejącym zapaleniem jelita grubego leczonych mesalazyną — trudny problem diagnostyczny. Seria przypadków i przegląd literatury

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Abstract

Pulmonary involvement in the course of inflammatory bowel disease has been a subject of interest to clinicians for long time, but despite this, its epidemiology and potential pathomechanisms remain obscured. Equally unclear is the role of medications used for bowel disease treatment in lung disease development. We present three patients with ulcerative colitis, all treated with mesalazine, in whom unexplained lung disease developed. Due to different clinical and radiological presentation, different conditions were initially placed on the top of the differential list in each of them. The outcome was favourable in all patients despite differences in management. We compared our patients with similar cases from literature. We show the level of difficulty and complexity in the issue of lung disease in patients with inflammatory bowel disease.

Key words: inflammatory bowel disease, ulcerative colitis, mesalazine, lung disease

Streszczenie

Zagadnienie zajęcia płuc w przebiegu nieswoistych zapaleń jelit pozostaje przedmiotem zainteresowania klinicystów od dawna. Pomimo to epidemiologia tego zjawiska ani potencjalne patomechanizmy nie są znane. Niewyjaśniona jest także rola leków stosowanych w zapaleniach jelit w rozwoju patologii płucnej. W pracy przedstawiono troje pacjentów z wrzodzącym zapaleniem jelita grubego leczonych mesalazyną, u których rozwinięła się choroba płuc. Z powodu różnej prezentacji klinicznej i radiologicznej, wstępna diagnostyka u każdego z nich ukerunkowana była na inne jednostki chorobowe. Zastosowane postępowanie u każdego z nich również było inne. Dokonaliśmy porównania naszych pacjentów do podobnych przypadków opisanych w literaturze. Opisani przez nas pacjenci dobrze obrazują, jak trudne i złożone jest zagadnienie chorób płuc rozwijających się u pacjentów z nieswoistymi zapaleniami jelit.

Słowa kluczowe: nieswoiste zapalenia jelit, wrzodziejące zapalenie jelita grubego, mesalazyna, choroba płuc

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Introduction

Ulcerative colitis (UC), Crohn’s disease and a subgroup of colitis difficult to classify constitute a group of inflammatory conditions called inflammatory bowel disease (IBD) [1, 2]. Nowadays, IBD is considered to be a systemic rather than exclusively gastrointestinal disorder. This is a consequence of the vast burden of information on so-called extraintestinal manifestations of IBD [3–6]. There is a common belief shared by gastroenterologists and chest physicians that the lungs are, although rarely, one of the targeted organs in IBD. It is, however, based on clinicians’ observations only. Unfortunately, no proper epidemiological investigations have ever been conducted to prove it, so the subject remains controversial. Storch et al. [7] have summarised more than 400 cases of pulmonary manifestations of IBD, published over a period of 50 years. Here, we enrich the literature on that subject by adding three more cases that support the hypothesis of a connection between IBD and pulmonary pathology, and show the complexity of the issue.

Case reports

Case 1

A 26-year-old, never-smoking, working as a shop assistant, Caucasian woman with UC was referred to our centre due to respiratory symptoms and abnormal findings in chest imaging studies. UC was diagnosed one year earlier. It had been treated with a three-month course of systemic glucocorticosteroids (GCs) at the beginning, and with oral mesalazine in a daily dose of 2.0 g for the last 8 months.

At the time of referral to our unit the bowel disease had been exacerbated for three months and dry cough, left-sided pleural chest pain and low-grade fever had been present for a month. Computed tomography (CT) of the chest performed 10 days before the admission showed multiple nodules and irregular masses scattered bilaterally in the lungs, thickening of the pleura and traces of fluid in the left pleural cavity; lymph nodes and remaining structures of the chest were normal. On admission she was apyrexial, and physical examination revealed pale skin, body mass index (BMI) 22.8, heart rate (HR) 100 beats per minute (bpm), blood pressure (BP) 130/65 mm Hg, respiratory rate (RR) 16/min, oxygen saturation (SaO₂) 99%, no enlarged peripheral lymph nodes, no peripheral oedema and no abnormalities on chest auscultation or abdomen palpation.

Blood tests showed leucocytosis 14.15 × 10⁹/L with neutrophilia 12.05 × 10⁹/L; eosinophils (eo) were normal. Erythrocyte sedimentation rate (ESR) was 115 mm/h, C-reactive protein (CRP) 63.4 mg/L (normal limit < 10), antinuclear antibody (ANA) titre 1:640 and anti-neutrophil cytoplasmic antibody (ANCA) negative. Renal and liver parameters as well as arterialised blood gases were normal. Chest X-ray (Fig. 1a) showed round-shaped shadows, the largest having a diameter of 33 mm localised in the lower field of the left lung, and features of fluid presence in both pleural cavities. The radiologic features, especially on CT scans, were suggestive of an inflammatory character of the changes, including bacterial, fungal and tuberculosis infection, but could also be seen in haematological malignancies. There were no abnormalities within the airways in a bronchoscopy; bronchial secretions were obtained for a broad spectrum of tests. Following this initial work-up the patient was given a 10-day course of an empirical antibiotic therapy (levofloxacin 500 mg bd orally). It resulted in normalisation of WBC (9.3 × 10⁹/L), but other inflammatory indices remained significantly increased (CRP 54.6 mg/L and ESR 120 mm/h). Microbiological and mycological cultures as well as tuberculosis tests (microscopic study, genetic probe) of bronchial secretions were negative and the cytology was irrelevant. There was no improvement on chest X-ray, and follow-up CT scanning (Fig. 1b) of the chest showed increase of the size of nodules when compared to a study performed one month earlier. At that stage a histological verification was required. The patient underwent left-sided video-assisted thoracoscopic resection of the mass from the left lower lobe. A microscopic examination revealed confluent active inflammation of the type of organising pneumonia with eosinophilic infiltrates, which in the opinion of the histopathologist could have been either associated with inflammatory bowel disease itself or drug (mesalazine) — induced. The cessation of mesalazine and treatment with systemic GCs were intended. The patient, however, declined the offered management and decided to continue to take mesalazine.

At a 3-months follow-up visit her condition was significantly improved, symptoms relating to the respiratory system disappeared. She still suffered from intestine-related problems. Blood tests were within normal limits. Chest X-ray revealed the regression of changes seen before, with only residual linear scars in the lower zone of the left lung. Pulmonary function tests showed
normal values of volumes and DLCO remained at the level of 70% of predicted.

Case 2

A 31-year-old, never-smoking, working in an office Caucasian man with UC diagnosed five years earlier, treated for this reason with oral and rectal preparations of mesalazine, having features of mild exacerbation of the intestinal disease for the last few days, presented with dry cough, right-sided chest pains of pleural type and fever. The symptoms had been present for 3 weeks and had not responded to an antibiotic and inhaled bronchodilators prescribed by his GP. Chest X-ray performed two weeks after the onset of the disease showed subpleural opacities in the middle/lower field of the right lung. Chest X-ray repeated one week later (Fig. 2a) revealed progression of these abnormalities.

The patient’s condition at the time of admission to the hospital was fair; he was afebrile but suffering from oppressive dry cough and pleural pain. Physical examination revealed BMI 23, HR 98 bpm, BP 140/90 mm Hg, RR 18/min, SaO₂ 97%, peripheral lymph nodes were not enlarged and peripheral oedema was not present. Normal vesicular breathing sound was heard on chest auscultation; however, it was slightly reduced at the base of the right lung. Blood tests were as follows: WBC 16.47 × 10⁹/L, neu 9.9 × 10⁹/L, eo 2.24 × 10⁹/L, ESR 80 mm/h, CRP 27.5 mg/L, ANA titre 1:160 and ANCA negative. Renal and liver parameters as well as arterialised blood gases were normal. Pulmonary angiography CT (Fig. 2b) was performed because a pulmonary embolism was one of the differential diagnoses. No contrast filling defects within the pulmonary artery bed were found. However, the lung window of the CT study showed multiple subpleural parenchymal consolidations in the right lung. No mediastinal lymphadenopathy or pleural fluid was seen. Localisation and morphology of lung abnormalities were highly suggestive of organising pneumonia. Bronchofiberscopy was carried out showing normal airways. Bronchoalveolar lavage (BAL) was performed, and immunological cell differential was as follows: macrophages — 80.5% (normal > 90%), lymphocytes — 13.5% (normal < 10%), neutrophils — 5.5% (normal < 3%), eosinophils — 0.5% (normal < 0.5%). Lymphocyte CD4+/CD8+ ratio was 2.74 (normal range 1.5–2.5). Other results of BAL fluid examination, i.e. microbiological cultures and cytology, were not relevant. Due to the patient’s cough and a characteristic picture of CT findings, transbronchial lung biopsy was considered not only unsafe but also unnecessary. Based on clinical and radiological presentation, high eosinophil count in peripheral blood, coexistence of UC and mesalazine intake, a diagnosis of organising pneumonia associated with either inflammatory bowel disease or, more probably, with mesal-
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Mesalazine toxicity was established. Mesalazine was stopped and treatment with oral prednisone 50 mg a day (0.6 mg/kg of body weight) and inhaled ciclesonide 320 micrograms bid (to relieve severe cough) was commenced. It resulted in an rapid improvement of the symptoms, normalisation of blood eosinophils count within three days, and partial resolution of changes on chest x-ray seen after one week of the treatment. The dose of prednisone was slowly reduced to 30 mg a day and the patient was seen again three months later. He was in good condition, free of any respiratory symptoms. Inflammatory indices were not elevated: ERS 5 mm/h, CRP < 5 mg/L, WBC was 11.29 × 10⁹/L and eosinophils count was 0.15 × 10⁹/L.

High resolution CT (HRCT) of the lungs showed complete regression of parenchymal lesions. Pulmonary function tests [not performed previously due to oppressive cough] showed: FEV₁, 103% of predicted value (pred), VC 104% of pred, FEV₁ /VC 0.84, RV 148% of pred, TLC 113% of pred, RV/TLC 0.31, DLCO 84% of pred. The patient was recommended to continue treatment with prednisone in decreasing doses until final withdrawal within another three months.

Case 3

A 65-year-old, retired, never-smoking Caucasian woman with UC was admitted to our Department due to respiratory symptoms and abnormal findings in imaging studies of the chest. UC had been diagnosed 2.5 years earlier. It had been treated with prednisone for a short initial period and, subsequently, with oral mesalazine for many months. The patient noticed exertional breathlessness one year prior to admission, but for the last six months it had been more troublesome. Sweating and body weight loss, 8 kg in total, also occurred. The patient’s daughter had pulmonary tuberculosis a couple of years earlier. For these reasons chest CT examination was carried out and it showed inhomogeneous attenuation of the lung parenchyma with irregularly scattered subtle interstitial patchy opacities, especially in the upper lobes and superior segment of the right lower lobe. At the time of exaggeration of respiratory symptoms, UC became active, too.

Shortly after the aforementioned chest CT was performed, the patient was admitted to a gastroenterology department, where oral prednisone in a starting dose of 60 mg a day and 6-mercaptopurine were added to the treatment. It resulted in improvement of both bowel and respiratory symptoms.

The patient presented to our unit three weeks after discharge from the gastroenterology department. She continued on prednisone (55 mg/day), 6-mercaptopurine and oral mesalazine 3 g/day. Her exertional breathlessness was improved and she was free of intestinal symptoms. She had normal body temperature, BMI 27.6, HR 84 bpm, BP 130/80 mmHg, RR 16/min, SaO₂ 96%, no enlarged peripheral lymph nodes, no peripheral oedema and no abnormalities on chest auscultation or abdomen palpation. Blood cell count, renal and liver parameters and arterialisled blood gases were normal. ESR was 11 mm/h, CRP 6.3 mg/L, ANA titre 1:100 and cANCA was positive.

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in titre 1:40. There were no significant alterations in chest X-ray. CT scan showed partial regression of previously seen diffuse interstitial abnormalities, subtle centrilobular nodules were still present in the upper lobes (Fig. 3). Pulmonary function tests revealed irreversible mild airway obstruction and hyperinflation of the lungs (FEV₁, 78% of predicted, VC 115% of predicted, FEV₁/VC 0.65, RV 170% of predicted, TLC 129% of predicted and RV/TLC 0.56) with normal DLCO (75% of predicted). BAL fluid differential count was as follows: macrophages 58.1%, lymphocytes 39.4%, neutrophils 2.5% and eosinophils 0.0%. Lymphocyte CD4+/CD8+ ratio was 3.4. Transbronchial lung biopsy was planned but could not be performed due to the patient’s poor cooperation. Microscopic examination of BAL fluid for acid-fast bacilli was negative, but the genetic probe was positive. The culture was ultimately inconclusive as it was contaminated. Blood T-SPOT TB test yielded a negative result. This fact and the significant clinical and radiological improvement on prednisone therapy were clear evidence against infectious aetiology, including tuberculosis. A watchful waiting attitude was adopted and the patient was recommended to continue with treatment according to the plan of the gastroenterologists in charge. She has been seen in our Department twice since then. During one-year follow-up she remained free of respiratory symptoms, her chest X-ray stayed stable and DLCO fluctuated slightly around 70% of predicted. The respiratory symptoms did not recur even when prednisone was stopped and she continued treatment with mesalazine.

Discussion

The differential diagnosis of pulmonary pathology in patients with inflammatory bowel disease embraces: infections, including opportunistic ones in patients taking GCs and/or other immunosuppressive agents, pneumonitis associated with IBD, pulmonary complications induced by used medications, and thromboembolic disease. Additional considerations are related to the presence of ANA and/or ANCA, frequently seen in association with IBD [8–11]. Differentiation is usually challenging, as it was in the presented cases. In addition, there is no specific marker or a single test that could differentiate between a coincidental pulmonary disorder and one potentially related to IBD or a drug-induced one. Establishing the ultimate diagnosis involves a broad set of additional investigations and a dose of clinician’s arbitrary opinion.

All the presented patients suffered from ulcerative colitis, the diagnosis of which preceded occurrence of respiratory system disease by one year in case 1, five years in case 2 and two and a half years in case 3. All had been treated with oral mesalazine when respiratory disease occurred; the duration of the treatment ranged from eight months (case 1) to five years (case 2). Patient 2 was using mesalazine rectal suppositories in addition to its oral preparation. In Patient 1, respiratory symptoms developed one month after the beginning of UC flare, in Patient 2 concomitantly with mild UC exacerbation, while Patient 3 suffered from exertional breathlessness for several months before a flare of UC. Presentation
of Patient 1 and 2 shared a lot of similarities, with an acute beginning and domination of cough, pleural chest pain and fever, whereas in Patient 3 prolonged exertional dyspnoea, sweats and body weight loss were the main symptoms. All of them had abnormal lungs in imaging studies. The review of 27 published cases [12–33] of IBD patients (19 UC and 8 Crohn’s disease patients) treated with oral mesalazine, in whom lung disease developed, showed that presentation of our patients was typical. The most common symptoms reported in the literature included: exertional breathlessness (22/27 patients), fever (18/27 patients), cough (18/27 patients), pleuritic chest pain (8/27 patients), body weight loss (4/27 patients) and sweats (2/27 patients). In 12 (44%) patients a triad of breathlessness, fever and cough was present. The median duration of exposure to mesalazine was 8 months (range 2 days — 8 years). Respiratory disease appeared in association with IBD flare as well as in the period of its quiescence. Our patients were in good/fair condition and had normal blood gases, but the literature shows that a vast proportion of similar patients presented with hypoxaemia of varying degree, some of them requiring admission to an intensive care unit [25, 33]. Data on imaging studies (chest X-ray, CT scanning) were given for 25 of the reviewed patients. Bilateral changes were seen in 21 patients, unilateral changes (interestingly right-sided in all cases) in 3 patients and in 1 patient imaging studies were normal. The broad spectrum of radiological findings, from the subtle thickening of the interstitium through centrilobular nodules, ground glass opacities, nonspecific opacities (migratory in one case) to multiple pulmonary nodules, was seen. Pleural fluid was present in three cases. Similarly, each of our patients had a different radiologic pattern of the lung. In Case 1, bilateral nodules and pleural effusion were present. In Case 2, multiple subpleural consolidations were seen in the right lung and in Case 3, centrilobular nodules were present. Data on WBC and blood eosinophilia were available for 16 reviewed IBD patients. In 10 patients the number of eosinophils in the blood was normal. In 6 patients it was elevated (in one of them eosinophilia was present before mesalazine commencement). BAL fluid examination, available in 10 patients, showed diversity of patterns. In different cases the domination of neutrophils [23], lymphocytes [20] or eosinophils [22] could be seen, but most frequently a mixed pattern was present. Not all patients with blood eosinophilia had high eosinophil counts in BAL fluid [22, 30, 31], and some patients with increased eosinophils in BAL fluid had normal eosinophil counts in the blood [17–20]. The results of histological examination of lung biopsy were available for 15 of 27 reviewed patients. Again, a diversity of patterns was present: eosinophilic pneumonia in two patients [15, 22], organising stage of eosinophilic pneumonia with eosinophilic infiltrates in one patient [19], features of organising pneumonia in five patients [12, 23, 24, 33], non-necrotising granulomas and scattered giant cells or giant cells alone in three patients [20, 23, 29] and interstitial fibrosis in two patients [18, 23]. Only one of our patients had histopathological verification. It was Patient 1, in whom microscopic examination of resected pulmonary nodule revealed organising pneumonia with eosinophilic infiltrates. Camus et al. [34] noted that organising pneumonia in IBD patients differed from cryptogenic organising pneumonia by the richer eosinophilic infiltrates, independent of taking or not taking medication suspected to cause lung injury.

Due to their presentation, typically with new-onset dyspnoea, fever, cough, changes in chest X-ray and elevated indices of inflammation, a chest infection was first suspected in our patients as well as in the other patients from the literature. As a consequence, an empirical antibiotic therapy and an effort to identify a causative microbiological factor was the first-line management. Very rarely in those patients cultures yielded a positive result, but even in those cases use of proper antibiotics failed to bring any improvement. Pulmonary tuberculosis is one of the major considerations in these patients, especially in patients with more insidious onset of pulmonary and general symptoms and a history of immunosuppressants use. Patient 3, with a history of a pulmonary tuberculosis in a family member, GCs use in the past and chronic breathlessness, sweats and weight loss as presenting symptoms, was a good example of such a situation. Diagnostic tests for tuberculosis in that patient gave confusing results with negative direct microscopic examination of BAL fluid and negative blood T-SPOT TB test, on one hand, and a positive genetic probe and inconclusive culture of BAL fluid, on the other hand. This patient was given treatment with GCs for UC flare, which resulted in a significant improvement of respiratory symptoms and radiological picture, which in our opinion was clear evidence against tuberculosis.

In Patient 1, the radiological picture of multiple masses in the lungs and very high ESR aroused concerns about a haematological mali-
gnancy as a cause. In Patient 2, chest pain and triangular-shaped subpleural opacities in the chest X-ray as well as an antibiotic failure directed differential thinking towards a pulmonary embolism with pulmonary infarctions. IBD is a well-recognised risk factor for thromboembolic disease [35–38]. Use of additional diagnostic tools such as histopathological examination of lung biopsy in one case and pulmonary CT angiography in the other case, made it relatively easy to exclude these conditions. It was more difficult to decide whether the pulmonary pathologies in our patients developed independently of the intestine disease and mesalazine action, or in connection with either of them. No conclusive proof exists either for a connection between lung pathology and IBD, or for a connection between lung pathology and mesalazine. Mesalazine together with its predecessor, sulphapyridine, are the main representatives of anti-inflammatory agents based on 5-aminosalicylic acid (5-ASA). In the German registry [39] 70% of patients with UC were treated with those medications. Sulphasalazine is well known for its clinically important side effects, which affect up to 20% of users and include gastroenterological manifestations, hepatic dysfunction, skin rashes, arthralgia and fever. The most serious toxicity, however, is associated with blood dyscrasias and, less frequently, with pulmonary pathology. Parry et al. [40] summarised 50 patients reported in the literature in the years 1972–1999 as possible cases of sulphalazine-induced lung toxicity. Sulphasalazine consists of 5-ASA in conjugation with sulphapyridine, and the letter component was thought to be responsible for the majority of side-effect reactions. Mesalazine, which does not contain the sulphur moiety, was introduced with hope to reduce systemic side effects and allergic reactions. Unfortunately, mesalazine appeared to cause adverse effects in around 3% of users, mostly headaches, diarrhoea, nausea and worsening of the colitis [41]. The incidence of mesalazine-induced lung disease is unknown. As mentioned above, hypotheses on a connection between mesalazine and pulmonary disease are based on clinical observations, and those are confusing. Evidence in favour of the hypothetical toxic effect of mesalazine found in the reviewed papers included: 1) continuation of mesalazine administration, even in a reduced dose or even if GCs were added, caused worsening of clinical condition, hypoxaemia, opacities on chest X-ray and pulmonary function tests in some patients [14, 20, 22, 25, 30, 32]; 2) lymphocytes stimulation test or basophile degranulation test for mesalazine yielded positive results in some patients [13, 19, 28]; 3) clinical and radiologic symptoms resolution was observed, usually within days or weeks from mesalazine discontinuation [13–15, 17–19, 27]; 4) reintroduction of mesalazine caused recurrence of symptoms within 2 days to 2 weeks in some patients [20, 21, 27]; and 5) in some patients with a history of previous toxicity of sulphasalazine, mesalazine caused the same effects [16]. In contrast, however, the following arguments question the contribution of mesalazine to the development of lung pathology: 1) successful reinstitution of mesalazine after an episode of its supposed lung toxicity in some patients [17, 33]; 2) complete resolution of pulmonary problems without mesalazine cessation or any other action in some patients [29, 34], even in patients with positive mesalazine lymphocyte stimulation tests [28]; and 3) occurrence of clinically, radiologically and histopathologically identical pulmonary disease in IBD patients not exposed to 5-aminosalicylic acid derivatives [24, 29, 34, 42–48]. Blood eosinophilia is considered to be a factor suggestive of drug-induced reaction. However, there are cases showing that not only blood eosinophilia but also BAL eosinophilia and even eosinophilic pneumonitis may occur in IBD without connection to medications [34]. The role of eosinophils in IBD has been noted but not fully understood [49].

As our review of the literature showed, pulmonary disease in IBD patients responded well to GCs, but spontaneous regression was seen in numerous patients as well. Most commonly mesalazine cessation and treatment with GCs were applied resulting in a rapid improvement [12, 23, 26, 31–33]. This approach was applied in Patient 2, in whom mesalazine was stopped and GC was commenced. Mesalazine suppositories were withdrawn as well, as there are some reports suggesting a relationship between this type of mesalazine preparation and lung toxicity [50, 51]. Patient 1 decided to continue with mesalazine and declined treatment with GCs. Patient 3 was treated with GCs and subsequently with other immunomodulatory drugs in addition to mesalazine, due to IBD activity. In all of them the outcome in terms of respiratory system disease was good.
Conclusions

Pulmonary pathology in patients with ulcerative colitis treated with mesalazine remains an interesting subject for further investigation.

Conflict of interest

The authors declare no conflict of interest.

References:


