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CASE REPORT

Recognising the risk of aspirin-sensitive respiratory disease in a patient with asthma who has previously tolerated aspirin

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Abstract

Asthma is a common chronic condition composed of numerous different phenotypes. One clinically relevant phenotype is that of aspirin-sensitive respiratory disease (ASRD) which is more frequently seen in patients with difficult asthma. Reliance on a history of previous reaction to non-steroidal anti-inflammatory drugs (NSAIDs) in order to diagnose ASRD may give false reassurance. We describe the case of a 58-year old man with late onset asthma who was suspected to have ASRD on the basis of associated clinical features despite having taken aspirin safely in the past. The diagnosis of ASRD was subsequently confirmed by an inadvertent aspirin challenge which led to a serious adverse asthma outcome.

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Introduction

Asthma affects over 5 million people in the UK today.[1] It is now widely recognised that this common chronic condition is actually a heterogeneous disorder that comprises numerous different phenotypes.[2] Characterisation of such phenotypes is an evolving area but one clinically relevant phenotype is that of aspirin-sensitive respiratory disease (ASRD). Aspirin (acetylsalicylic acid) is among the most easily accessible and widely used medications today. Yet in the century since its creation, significant adverse effects of aspirin on the respiratory tract have been identified. Widal[3] initially reported an association between aspirin sensitivity, asthma and nasal polyposis in 1922, which Samter[4] further characterised as the "asthma triad" many years later.

ASRD may be associated with treatment-resistant "difficult asthma". Clinicians should be alerted to the presence of this phenotype by a history of onset of asthmatic symptoms within three hours of ingesting non-steroidal anti-inflammatory drugs (NSAIDs). However, most patients with asthma will have either previously tolerated these drugs or will have avoided them for fear of an adverse reaction. This poses a potential dilemma for clinicians looking after patients with asthma – i.e. how to assess the risk of ASRD in these patients. Is a previous history of aspirin tolerance a reliable indicator that a patient does not now have ASRD? There is no simple diagnostic test for this phenotype, but it is associated with particular clinical characteristics[5] including asthma onset in the 3rd or 4th decade, chronic rhinitis, nasal polyposis, urticaria, angioedema, plus development of NSAID intolerance. Prompt recognition of ASRD could identify a troublesome asthma phenotype, facilitate appropriate avoidance of aspirin and NSAIDs, and prevent potential poor asthma outcomes.

We present a case to illustrate the importance of considering the diagnosis of ASRD even in the absence of a previous adverse reaction to NSAID.

Case history

A 58-year-old man was referred to a secondary care asthma clinic for specialist review. He had no history of childhood or

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early adult asthma, eczema or rhinitis, but he reported developing persistent rhinitis with polyposis in his 30s and mildly symptomatic asthma at the age of 40. Over the two years prior to review, asthma control had declined with frequent exacerbations requiring oral corticosteroids. In that period he had needed several Emergency Department (ED) attendances and had been admitted to hospital twice. By the time of his clinic attendance he was using salbutamol nebulisers twice daily plus inhaled salbutamol four times a day. His exercise tolerance was 200 yards on the flat before becoming symptomatic. Other triggers included exposure to strong fragrances, smoke and cats, plus ingestion of alcohol and chocolate. He had previously taken NSAIDs without symptoms but had not done so recently. Other co-morbidities included perennial rhinitis and gastro-oesophageal reflux. He was an ex-smoker of 10 pack-years. He had given up work as a chef as his condition worsened.

On examination in clinic he appeared breathless and wheezy. He had mild clubbing. Nasal inspection revealed marked nasal mucosal congestion and bilateral polyposis (despite previous polypectomy). Chest examination demonstrated bilaterally reduced expansion plus wheeze. Spirometry confirmed severe airflow obstruction with an FEV_1 of 1.06L (30% predicted) and 11% bronchodilator reversibility. Skin prick testing revealed sensitisation to cat, dog, *Alternaria, cladosporium* and chocolate. His total IgE (1186) and eosinophil count (2.7) were raised, but specific IgE to aspergillus, ANCA, and alpha-1-antitrypsin were normal.

Although the patient had previously tolerated NSAIDs, given the triad of late onset difficult asthma, preceding chronic rhinitis and recurrent nasal polyposis, a diagnosis of dual salicylate (aspirin) sensitive and atopic asthma was suspected. Over time, the patient's treatment was progressively modified to incorporate ultrafine particle inhaled corticosteroid (ICS), long-acting β_2-agonist (LABA), leukotriene antagonist (LTRA), nasal corticosteroid, antihistamine, gastro-oesophageal reflux therapy (proton pump inhibitor and H2 antagonist) and low dose maintenance oral corticosteroid. He was advised to avoid NSAIDs and also undertook a supervised low salicylate diet.

However, his asthma control remained variable. Further investigations identified minor bronchiectasis in the right lower lobe on high resolution computed tomography (HRCT) scanning of the chest, but normal endobronchial appearances at bronchoscopy. Upper GI endoscopy demonstrated a small hiatus hernia, and oesophageal pH monitoring showed mild gastro-oesophageal reflux. After 18 months follow-up, the patient was hospitalised with another significant exacerbation. During that admission he developed acute chest tightness, breathlessness and tachycardia resulting in urgent review by on-call junior medical staff. A diagnosis of possible acute coronary syndrome was made. He was transferred to the Coronary Care Unit, the diagnosis of suspected ASRD was not noted, and he was given aspirin (300mg). Despite being warned about salicylate sensitivity in the clinic, since he had never reacted to aspirin in the past he took the aspirin without question. He rapidly developed widespread urticaria followed by angioedema, throat closure, wheeze and hypotension. These symptoms were treated with intravenous steroid, antihistamine, nebulised bronchodilator, oxygen and intramuscular adrenaline to good effect. An adverse reaction to aspirin was diagnosed after further scrutiny of his medical notes. Subsequently, his asthma settled and cardiac investigation showed normal stress echocardiography without evidence of inducible ischemia. Further cardiology tests were not pursued. After a brief admission, the patient went home with further outpatient follow-up for his asthma.

Discussion

This case illustrates the important learning point that a history of previous tolerance of NSAIDs may give misleading reassurance about the safety of taking aspirin for certain asthma patients. It also suggests the equally important learning point that awareness of associated phenotypic features might aid diagnosis of ASRD in a clinical setting despite the absence of previous reactions to NSAIDs.

ASRD affects a minority of asthmatic patients, though patients with asthma are generally advised to avoid NSAIDs owing to the difficulty in identifying who is at risk of ASRD. ASRD prevalence depends on the method used for diagnosis. Questionnaires estimate a prevalence of 0.6–2.5%[6,7] in the general population and 3.8–11%[7,8] in patients with asthma. However, direct provocation tests with aspirin in asthmatic populations have revealed a far higher prevalence of 21%.[9] This suggests that relying on a history of previous reaction to NSAIDs may significantly underestimate the true extent of this problem and that there could be many asthmatics with unrecognised ASRD. Clinicians need to be able to recognise accurately which asthma patients are likely to possess an ASRD phenotype so that they can emphasise appropriately the importance of NSAID avoidance to those individuals.

ASRD pathogenesis is complex and not yet fully defined. It is not IgE-mediated, but is associated with disordered arachidonic acid metabolism with impaired cyclo-oxygenase function, overproduction of cysteinyl leukotrienes (CystLTs) and increased $CystLT_1$ receptor expression.[10] Anti-inflammatory drugs which exacerbate ASRD selectively inhibit the cyclo-oxygenase-1 (COX-1) enzyme. Conversely drugs selectively inhibiting the COX-2 enzyme appear to be tolerated by most patients, with ASRD offering potentially safe alternative analgesia.

The optimal diagnostic test for ASRD[11] remains medically-supervised oral aspirin challenge. This carries potential risk and has significant resource implications[12] for a typical District General Hospital setting. Diagnostic inhalational and nasal aspirin challenges are also possible but require referral to a specialist centre. In this case, an inadvertent challenge confirmed the diagnosis of aspirin sensitivity in our patient who had never reacted to aspirin before. Nevertheless, the diagnosis of ASRD had been suspected from associated clinical features 18 months prior to this episode. Based on that clinical suspicion, advice had been issued to avoid NSAIDs in this patient and if that advice had been followed a potentially life threatening reaction could have been averted.

ASRD usually presents with persistent rhinorrhoea and nasal congestion which is followed a few years later by asthma, nasal polyposis and often relatively late by adverse reactions to NSAIDs.[3] The typical age of onset of initial symptoms is between 30-35 years.[13] Women tend to be affected more[14] and often present earlier. Many ASRD patients are non-atopic. Where atopy is present, rhinitis and asthma occur at a younger age while aspirin intolerance and polyposis develop at similar times regardless of atopic status.[5] Our patient demonstrated acute urticaria, angioedema and anaphylactic shock in response to aspirin exposure. Such a dramatic reaction on aspirin exposure is uncommon in patients with ASRD, with anaphylactic shock occurring in 6% of cases.[5]

ASRD is associated with chronic severe asthma and occurs in 25% of patients intubated for asthma on Intensive Care Units.[15] Compared to aspirin tolerant asthmatics, patients with ASRD have a tendency towards irreversible airways obstruction[16] and poor response to corticosteroids.[17] In terms of rhinitis, those with ASRD have worse disease, with larger volume of polyp tissue, and higher polyp and symptom recurrence rates post resection.[18]

Chronic management of ASRD follows conventional recommendations for asthma[19] and rhinitis.[20] Avoidance of aspirin and NSAIDs is vital to avert potentially severe episodes. Despite such avoidance many patients show unstable asthma. Salicylates occur naturally in foods,[21] and dietary exposure may be relevant in some patients.[22] Avoidance of dietary exposure can be tried but with a limited evidence base. Aspirin desensitisation offers another mode of therapy in some situations,[23] and may have been appropriate in our patient if coronary artery disease had been identified.

Conclusions

ASRD is a clinically significant asthma phenotype that all healthcare professionals who care for patients with asthma should be aware of. ASRD is associated with "difficult asthma" and lack of awareness of the nature of ASRD may lead to serious adverse asthma outcomes. This case illustrates the important learning point that a history of previous tolerance of NSAIDs may give false reassurance about the safety of taking aspirin for certain asthmatic patients. It also suggests that awareness of associated clinical features might help raise suspicion of ASRD in a clinical setting despite the absence of previous reactions to NSAIDs (see Box 1).

Box 1: Learning Points

- Aspirin Sensitive Respiratory Disease is associated with Difficult Asthma
- A history of previous tolerance to Non-Steroidal Anti-Inflammatory Drugs may give false reassurance about the safety of taking aspirin for certain asthmatic patients.
- Clinical features may help identify ASRD in a clinical setting despite the absence of previous reactions to NSAIDs.
- Relevant clinical characteristics for ASRD include asthma onset in the third or fourth decade, chronic rhinitis, nasal polyposis, urticaria, and angioedema.

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Conflict of Interest Statement

There were no conflicts of interest for the authors during the preparation of this manuscript.

Authorship and Contributorship

DA came up with the idea of writing the manuscript, performed a literature search and wrote the first draft of the manuscript. RJK identified and managed the case reported, supervised the writing of this manuscript and acts as guarantor for the final paper.

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