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Polypoid rhinosinusitis in patients with host defence deficiencies: Cellular infiltration and disease severity*

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SUMMARY

Polypoid rhinosinusitis is a chronic inflammatory, mucosal disease. Eosinophils may play a key role in driving and maintaining this inflammation. Polyps in conditions associated with chronic infective rhinosinusitis – such as cystic fibrosis (CF) and primary ciliary dyskinesia – however have been described as neutrophilic. We compared cell counts in polyps from 55 patients with host-defence deficiencies (HDD) to polyps from 50 patients without HDD. The CT-scan appearance was also compared to the cell counts in the HDD group. No difference was detected in the percentage of patients with eosinophils from either group. Significantly more patients in the HDD group had polyp neutrophils ($p<0.001$). Non-HDD-patient polyps contain more eosinophils ($p<0.000$) whilst HDD-patient polyps contained more neutrophils ($p=0.005$) and plasma cells ($p=0.05$). Significant correlation was found between the neutrophil count and the CT score ($p=0.012$) and the mast-cell count and the CT score ($p=0.02$). Eosinophils are present in HDD and non-HDD polyps. Whilst the degree of cellular infiltration may vary, to classify polyps as eosinophilic or neutrophilic may be a false distinction.

Key words: host defence deficiency, polyposis, eosinophils, neutrophils

INTRODUCTION

Sinonasal polyposis has traditionally been considered infective (Skillern, 1913) and after descriptions of eosinophilic infiltration, allergic (Neivert, 1942) in origin. The inaccuracy of this simplistic approach to aetiology is now well recognised (Jankowski, 1996). In particular mast cells (Larocca et al., 1989; Mygind, 1990) and eosinophils (Frenkiel et al., 1982; Ogawa, 1986; Feather and Wilson, 1995; Jordana et al., 1995; Stoop et al., 1993) are thought to have key roles in polyp formation via mechanisms that are not allergen/IgE-dependent.

Nasal polyposis is also recognised as occurring in patients with respiratory tract sepsis due to host-defence deficiencies (HDD) such as cystic fibrosis (CF; Rowe-Jones and McKay, 1996), primary ciliary dyskinesia (PCD; Greenstone et al., 1985), and Young's syndrome (Schanker et al., 1985). We have also identified polyposis in patients with sinobronchial syndrome due to primary immunoglobulin deficiency.

Several authors (Mygind, 1979; Settipane, 1991; Jordana et al., 1995) have anecdotely described polyps as neutrophilic or eosinophilic, distinguishing those occurring with HDD from the remainder. As suggested by Maran and Lund (1990) this differentiation is probably not so clear-cut and we have therefore reviewed the cellular infiltration in polyps removed during endoscopic sinus surgery (ESS) from 55 patients with HDD.

In asthma, the degree of eosinophil infiltration correlates positively with the severity of disease (Wardlaw et al., 1988). We have therefore also related the cell counts in the HDD population to the extent of disease demonstrated on pre-operative paranasal sinus CT scan.

MATERIAL AND METHODS

We have performed ESS on 63 patients with an HDD and chronic, polypoid rhinosinusitis since 1989. The diagnostic groups are displayed on Table 1. These diagnoses were identified after screening in the host-defence deficiency unit at the Royal Brompton Hospital. The investigative protocol included as indicated sweat tests, nasal potential difference measurements and genetic analysis for cystic fibrosis, immunoglobulin levels including subclasses, nasal and pulmonary ciliary beat frequency and analysis of ciliary ultrastructure. Haematoxylin and eosin (H/E) stained polyp sections were available for review from 55 patients (30 male and 25 female). The mean age of these 55 patients at

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Table 1. The range of host-defence deficiencies and the number of patients with each diagnosis undergoing endoscopic sinus surgery and histological review.

host-defence deficiency	ESS	histology reviewed
Ig major class deficiency:	4	4
(IgG)	(1)	
(IgA)	(2)	
(IgG+IgA+IgM)	(1)	
cystic fibrosis	50	44
primary ciliary dyskinesia	8	6
Young's syndrome	1	5
total	63	55

the time of surgery was 24.7 years (SD: 9.4 years) with 12 patients aged 16 years or less.

Twenty-eight patients were receiving long-term systemic antibiotics prior to surgery. Eleven patients had undergone heart-lung transplants and were receiving maintenance prednisolone, azathioprine and cyclosporin. One further patient was receiving long-term prednisolone as well as antibiotics for lower respiratory tract disease. The four patients with major immunoglobulin-class deficiencies were receiving regular intravenous immunoglobulin. All patients had failed medical treatment with topical nasal corticosteroids and multiple antibiotic regimens prior to referral for ESS. The patients undergoing surgery therefore represent those who had the severest disease and had failed to significantly respond to medical management. Consequently, at the time of their surgery only 4 patients were using topical nasal steroids.

The control group comprised 50 patients (37 male and 13 female) recruited prospectively, all of whom who were undergoing ESS for bilateral polyposis. The mean age of this group was 44 years (SD: 11 years). None of these patients had lower respiratory tract suppuration or a history consistent with CF or other HDD. The youngest age at presentation was 20 years. This patient underwent sweat tests which were normal. Twenty-three patients had asthma, which was aspirin-sensitive in four individuals. None of the control group had used topical nasal steroids for at least three weeks prior to surgery and none had taken systemic steroids for at least two months prior to surgery. CT scans were performed on all patients prior to ESS using a standard protocol (Rowe-Jones et al., 1995) and were assessed and staged according to the system described by Lund and Mackay (1993).

Polyp specimens reviewed had all been routinely fixed, cut to 4-μm thickness and stained with H/E. Sections were chosen randomly and examined by the pathologist without knowledge of clinical data. A stage graticule was used to calculate the area of the field of view at ×400 magnification. Sixteen squares of a representative area of inflammatory infiltrate density were counted with relation to eosinophils, neutrophils, lymphocytes, plasma cells, monocyte/macrophages and mast cells. These counts were converted to the number of cells per mm^2 and percentages. For patients with more than one section of polyp specimen, the above count method was repeated for each slide and an average value obtained. Statistical analysis was performed with Statworks™ version 1.2. Data comparison was with Chi-squared and unpaired *t*-tests. Data not normally distributed was log transformed after addition of a constant before *t*-test comparison.

Table 2. The number of patients with each cell type present in their sinonasal polyp tissue (number in parentheses is percentage).

	eosinophil	lymphocyte	plasma cell	mast cell	macrophage	neutrophil
HDD (n=55)	52 (94)	55 (100)	55 (100)	52 (94)	48 (87)	54 (98)
Non-HDD (n=50)	47 (94)	50 (100)	47 (94)	40 (80)	37 (74)	34 (68)
x^2 test			$0.05<p<0.1$	$p<0.025$	$0.05<p<0.1$	$p<0.001$

HDD: host defence deficiency

Table 3. The mean number of each cell type present per mm^2 of sinonasal polyp tissue from patients.

	eosinophil	lymphocyte	plasma cell	mast cell	macrophage	neutrophil	total
HDD							
mean	261.3	1421.8	939.7	117.7	127.6	449.6	3,172.8
SD	561	1105.4	1239.5	151.4	277.6	448.9	2,211
Non-HDD							
mean	910	1198.3	649	89.8	93.8	234.1	3,156.9
SD	986.8	1089.2	925	94.7	139.2	292.9	2,411.4
t-test							
t-statistic	−4.64	1.04	1.98	1.11	0.771	2.86	−0.04
significance	0.000	0.303	0.05	0.26	0.44	0.005	0.97

HDD: host defence deficiency, SD: standard deviation

RESULTS

The number of patients with each cell type present, for the HDD and non-HDD groups is seen in Table 2. No significant difference exists in the number of patients with eosinophils, lymphocytes, plasma cells or macrophages between the two groups. However, significantly more patients in the HDD group have neutrophils and mast cells present in their polyps.

The mean cell numbers are demonstrated in Table 3. Normality assessment revealed non-normal distribution for HDD macrophage, plasma-cell and eosinophil counts and non-HDD plasma cell counts. The data for these cell types was therefore log transformed after addition of a constant. No significant difference was found in the total number of cells for either groups. Non-HDD-patient polyps contained significantly more eosinophils whilst HDD-patient polyps contained significantly more neutrophils and plasma cells.

CT scans were available for review in 46 of the HDD patients. Simple, linear regression analysis revealed a significant correlation between the neutrophil count and the CT score (*t*-test for hypothesis of zero slope; t statistic 2.6, p=0.012) and the mast-cell count and the CT score (*t*-test for hypothesis of zero slope; t statistic 2.41, p=0.02).

DISCUSSION

Host-defence deficiencies are classically associated with chronic respiratory tract sepsis in the form of bronchiectasis and rhinosinusitis (Mackay et al., 1983). These result from impaired mucociliary clearance due to primary abnormalities of ciliary action, as in PCD, or abnormalities of the composition and properties of mucus, as in CF and Young's syndrome. Primary systemic immunodeficiency may also be responsible, in particular due to selective IgA, IgG and IgG subclass deficiencies (Knutsen, 1994; Scadding et al., 1994).

Polyposis is also described in association with PCD (Pedersen and Mygind, 1982; Greenstone et al., 1985), Young's syndrome (Schanker et al., 1985), CF (Rowe-Jones and Mackay, 1996) and in this series also with immunoglobulin deficiency. Some degree of sinus mucosal thickening, probably related to recurrent acute or chronic infection, is likely to be demonstrated on plain X-ray (Neely et al., 1972; Greenstone et al., 1988) and particularly on CT scan (Cuyler and Monaghan, 1989) of almost all patients with HDD. We have not found polyps during outpatient Hopkin's rod endoscopy in all our patients with these conditions. Other authors have described endoscopic detection of polyps in 45-51% of patients with CF (Brihaye et al., 1994; Coste et al., 1995) and without endoscopy in 33-40% of patients with PCD (Pedersen and Mygind, 1982; Levison et al., 1983). Thus, it cannot be definitively concluded that infection causes polyp formation in patients with HDD. However, in all our patients with HDD undergoing endoscopic sinus surgery, polyps and polypoid mucosa were found within the nasal cavities and/or within the sinus system cellular compartments.

Early workers realised that sinus mucosa inflammation, sometimes termed catarrhal, could occur without infection and be associated with hyperplasia and polyposis (Hajek, 1926; Neivert, 1942). Currently, as in asthma (Reed, 1995), evidence has accumulated that the eosinophil may play a central role in initiating, maintaining and regulating the inflammation and oedema of non-infective chronic rhinosinusitis and polyp formation (Harlin et al., 1988; Ohno et al., 1991, 1992; Finotto et al., 1992; Moneret-Vautrin et al., 1992; Stoop et al., 1993; Elovic et al., 1994; Feather and Wilson, 1995; Jordana et al., 1995). In our study we have found eosinophils in 94% of cases with polyps and HDD-related infection. Eosinophils may still therefore contribute to polyp formation in patients with HDD and chronic infective rhinosinusitis. Other authors have also described neutrophil infiltration in non-HDD polyps (Baumgarten et al., 1980; Hamilos et al., 1993). We therefore consider the neutrophil/eosinophil classification of polyps unhelpful.

The presence of significantly more neutrophils and plasma cells in patients with HDD is consistent with the presence of infection as well as polyposis. Theoretically, neutrophils might also contribute to polyp formation by the release of proteases and prolongation of inflammation (Hamaguchi et al., 1991). Experimental studies in rabbits also support the premise that sinus mucosal infection may result in polyp genesis (Fukami et al., 1993; Norlander et al., 1993). However, whilst the induced polyps were noted to be oedematous, containing numerous mononuclear inflammatory cells, no further indication of the type or extent of cellular infiltration was given.

Mast cells cause tissue oedema with eosinophil recruitment via degranulation – which need not be IgE-dependent – and release of histamine, arachidonic acid metabolites (Jung et al., 1987; Yamashita et al., 1989; Ruhno et al., 1990) and platelet-activating factor (Furukawa et al., 1992). Degranulated mast cells have been described in polyps including those from patients with CF (Drake-Lee, 1993). Degranulation may be related to cytokine release from $CD4^+$ T-lymphocytes (Larocca et al., 1989). Unlike in our study, Henderson and Chi (1992) found significantly more mast cells in CF polyps compared with non-CF polyps. Electron microscopy revealed evidence of spontaneous mast-cell degranulation in the CF, but unusually not the non-CF specimens.

Lymphocytes were the commonest cell type in both HDD and non-HDD polyps. Previous studies reveal nasal lymphoid cells in patients with polyps to be predominantly $CD4^+$ and $CD8^+$ T-cells (Larocca et al., 1989; Stoop et al., 1989, 1992). Lymphocytes are regulatory and effector cells in the inflammatory response and so may have important roles in polyp formation. In particular, T-cell-derived granulocyte/macrophage-colony-stimulating factor (GM-CSF) may contribute to eosinophil accumulation and activation (Jordana et al., 1995). GM-CSF is also released by monocytes (Jordana et al., 1995) and we found no significant difference in the number of these cells whether in polyps from HDD or non-HDD patients. Larocca et al. (1989) described activated $CD4^+$ T-cells in polyps. They suggested that $CD4^+$-derived interleukins 2, 3 and 4 were associated with mast cell maturation and activation and therefore polyp formation.

The degree of bronchial eosinophilic infiltration in asthma has been shown to correlate with the severity of the disease and the degree of bronchial hyperresponsiveness (Wardlaw et al., 1988). Kennedy (1992) has suggested that in chronic rhinosinusitis with and without nasal polyposis, the extent of sinus disease

demonstrated on CT scan correlates with outcome after ESS and hence with disease severity. We therefore compared the individual cell counts with CT-scan score. No correlation was found with the eosinophil counts, but a positive correlation existed between the CT score and neutrophil count. The neutrophilia may relate to suppuration. As CT scanning cannot clearly differentiate mucus and pus from polypoidal mucosa, we cannot however conclude that the neutrophils have a dominate role in polyp formation. Mygind (1990) has suggested that polyp pathogenesis may depend on mast cell degranulation and it is interesting that we have found the CT-scan extent of disease to correlate with the degree of polyp mast-cell infiltration.

Jordana et al. (1995) have suggested that the formation of nasal polyps is underpinned by a "tissue-driven response" to a range of initiating insults. The tissue cells such as fibroblasts and epithelial cells, release cytokines and growth factors, one result of which is eosinophil influx and activation. The activated eosinophil releases further cytokines resulting in autocrine loops of stimulation involving many of the cells of inflammation. Whilst we have not demonstrated that the extent of eosinophil infiltration relates to extent or severity of sinonasal polyposis it is possible that the state of activation of these cells, or their cytokine expression may (Ohno et al., 1991; Hamilos et al., 1993). Eosinophils may produce inflammatory and regulatory cytokines such as IL-3, IL-5 and GM-CSF. Nasal polyp samples have been shown to demonstrate significantly elevated levels of IL-5 (Hauser et al., 1996) and GM-CSF (Jordana et al., 1995).

We have not examined these factors in our study. We have found eosinophils in polyps from patients with and without HDD and consider the neutrophilic/eosinophilic distinction inaccurate and unhelpful. The role of tissue cells and eosinophils may be common to all polyp groups. The degree of infiltration of each cell type however may vary with the type of tissue insult in different patient groups.

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