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S33 DOES ANTI-REFLUX SURGERY SYMPTOMATICALLY IMPROVE EXTRA-OESOPHAGEAL SYMPTOMS AND QUALITY OF LIFE IN GASTRO-OESOPHAGEAL REFLUX DISEASE

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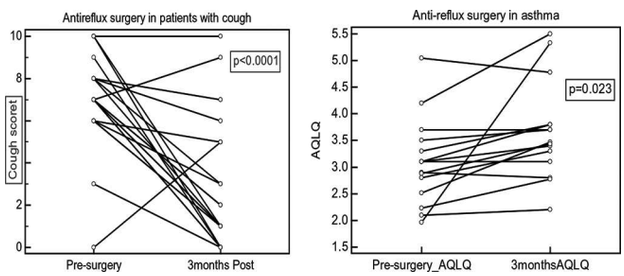
Introduction Extra-oesophageal (ie laryngeal, pharyngeal and pulmonary) symptoms of gastro-oesophageal reflux (GOR) are common clinical problems. GOR can cause a chronic cough and its prevalence is higher in asthmatics than in the general population. Proton pump inhibitors (PPI) are the most effective available therapy but in those who remain symptomatic despite optimal medical therapy anti-reflux surgery is considered.
Method At our central England teaching hospital a database was set up for all respiratory patients with GOR who were referred for anti-reflux surgery. Symptoms were assessed at baseline (pre-surgery), 3 months post surgery and 12 months post surgery using the asthma quality of life questionnaire (AQLQ, range; 0 = worst -7 = best) and a cough symptom questionnaire (range; 0 = no cough -10 worst cough).
Results A total of 61 patients (70% females) with mean age of 48.64 (range 20 - 78 years) were analysed. 34 patients were asthmatics and 26 patients had a chronic cough. 1 patient was excluded as they had vocal cord dysfunction.

All patients had significant GOR confirmed by oesophageal manometry and pH reflux studies [mean DeMeester score of 46.6 (SD = 38.4, normal range <14.72), hypotonic mean lower oesophageal sphincter pressure of 5.7 mmHg (SD 3.78, normal range = 12–25) and a mean% reflux time of 11.9 (SD 8.98, normal range <4%)]. The baseline mean FEV_1 in the asthma group was 2.08 (mean FEV1/FVC 0.72) compared to 2.61 (mean FEV1/FVC 0.81) in the cough group.

There was significant improvement in reflux symptoms. In the asthma group, the mean AQLQ score improved from baseline (3.05, SD = 0.8) to 3 months post surgery (3.68, SD = 0.9) (p = 0.0235), and 12 months post surgery (3.5, SD = 1.2) which did not reach statistical significance (p = 0.1) [see Figure 1]. There was also marked improvement in the cough symptom score from baseline (7.0, SD = 2.3) to 3 months post surgery (2.8, SD = 3.1) (p = <0.0001) [see Figure 1].
Conclusion In patients with evidence of severe GOR who remain symptomatic despite optimal medical management, anti-reflux surgery can improve cough and asthma related quality of life.



Abstract S33 Figure1 Does anti-reflux surgery symptomatically improve extra-oesophageal symptoms and quality of life in gastro-oesophageal reflux disease

S34 MANAGEMENT OF CHRONIC COUGH IN PRIMARY CARE

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Background Chronic cough is a common symptom in primary care. There appears to be significant variation in investigation and empirical treatment prior to referral on to secondary care. We looked at; a) Investigation/treatment undertaken prior to referral to secondary care and b) a survey of how GPs manage cough.
Method The study consisted of; a) Retrospective review of referrals (January 2012-January 2013) to a secondary care cough clinic and b) an online questionnaire on cough distributed to colleagues in primary care.
Results Of the primary care referrals, 47/58 casenotes were available (mean age was 59(27–84), 63% female). Only 4/47 (8.7%) were current smokers. Median duration of symptoms at referral was 7 months (2–420), 35/47(74.5%) had a chest X-Ray prior to referral, 18/47(39.1%) spirometry, 3/47 had used ACE inhibitors. Most investigations performed prior to referral were normal. Empirical treatment attempted included; antireflux therapy 23/47(50%), inhaled corticosteroids 12/47(26.1%) and nasal steroids 9/47(19.6%). Various other treatments were used (including cough suppressants, antihistamines, leukotriene receptor antagonists and antibiotics) in 22/47(46%).

Only 16/51(31%) of questionnaire respondents were aware of published cough guidelines. Most respondents were aware of the definition of chronic cough (37/51(72.5%)). When asked to list the 3 commonest causes of chronic cough, asthma was identified by 33 (64.7%), GORD by 38 (74.5%) and rhinitis/post-nasal drip by 20 (39.2%). Treatments most commonly initiated included acid suppression (PPI's) 33/51(64.7%), nasal spray 18/51(35.3%) and inhaled steroids 4/51(7.8%). The majority of patients do not get referred on to secondary care; 34/51(66.6%) of respondents estimate they refer less than 10% of cases. Referral was usually triggered by the following factors - unclear diagnosis, failed treatment, patient concern or abnormal tests.
Conclusions Many patients are referred on to secondary care without basic investigations and appropriate trials of recommended therapy. Knowledge of chronic cough in primary care is limited and most GPs are unaware of published guidelines. Increased education and awareness of cough guidelines could improve management of cough in the community. This is a topic that requires further systematic study as there is very little research in this area.

Cutting edge respiratory science

S35 MIF-CXCR4 AS A NOVEL AXIS FOR MESENCHYMAL STEM CELLS RECRUITMENT TO TUMOURS IN VIVO

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Mesenchymal Stem Cells (MSCs) are inherently tumour-homing, immunosuppressive and can be isolated, cultured, expanded, and transduced, making them viable candidates for cell therapy. MSCs can also be useful in allogeneic transplantation because of their immunocompatibility. MSCs have the capacity to home specifically to tumours including gliomas and breast, colon, ovarian, and lung carcinomas, among many other primary and metastatic tumours. Some discrepancies are however present regarding the mechanism and the involvement of molecules/receptors in MSC homing to tumours.

We have used in this study a combination of genome expression profiling and cytokine arrays to screen for candidates mediating MSC homing to two different cancer cell lines: A549 and MDAMB231. We found a variety of interleukines and cytokines already described as players in the process, such as IL6, IL8, CCL2. Additionally, from *in vitro* migration and invasion assays, we show that CXCR4 is a major player in this mechanism being the essential MSC receptor for the process to occur. Furthermore, we have identified MIF as the major trigger for MSC homing, being secreted from tumour cells at high levels.

For the first time, we have identified in this study a novel axis: MIF-CXCR4, showing a physical interaction between them and validating their essential role *in vitro* and *in vivo*. Importantly, knocking down the expression of CXCR4 in MSCs or MIF in tumour cells, drastically decreased MSC recruitment to tumours in a *in vivo* model of lung metastasis.

A better understanding of MSC homing players towards tumours will help the development of novel strategies in their use as vehicles in cancer cell therapy.

S36 DIFFERENTIATION OF TUBERCULOSIS AND SARCOIDOSIS BY TRANSCRIPTIONAL PROFILING OF IMMUNE RESPONSES IN MEDIASTINAL LYMPH NODE SAMPLES

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Introduction and Objectives Differentiating tuberculosis and sarcoidosis can be difficult, particularly in the context of mediastinal lymphadenopathy, because both diseases are characterised by overlapping clinical phenotypes and histologically similar granulomatous inflammation. Currently, diagnosis relies heavily on microbiological confirmation of tuberculosis which is only available in <50% of cases. Therefore, novel diagnostic strategies are needed to prevent morbidity associated with delayed or inappropriate treatment. We tested the hypothesis that genome wide transcriptional profiling of mediastinal lymph node samples obtained by minimally invasive endobronchial ultrasound guidance could identify gene signatures that differentiate tuberculosis and sarcoidosis.

Methods *In vivo* immune responses were compared in mediastinal lymph node biopsies obtained via endobronchial ultrasound guidance from patients with tuberculosis, sarcoidosis or non-granulomatous disease using genome-wide transcriptional profiling. Machine learning algorithms were used to test the discriminatory power of identified gene signatures which distinguished granulomatous from non-granulomatous disease or tuberculosis from sarcoidosis.

Results Comparison of lymph node genomewide transcriptional profiles by principal component analysis revealed clear differences between granulomatous and non-granulomatous disease. Granulomatous profiles showed significant enrichment for genes involved in antigen presentation, inflammatory responses, innate immune responses and T cell activation, in keeping with the processes involved in granuloma generation. As expected, sarcoidosis and tuberculosis sample profiles were very similar, however, significant gene expression differences were still evident between these two groups. In particular, several genes related to development of granuloma architecture were more highly expressed in sarcoidosis samples. Next we used machine learning tools in order to test the discriminatory power of differentially expressed gene signatures and found that the support vector machines algorithm correctly classified up to 97% of granulomatous and non-granulomatous disease cases. Importantly, this technique successfully distinguished sarcoidosis from tuberculosis in up to 100% cases.

Conclusions Transcriptomic analysis of lymph node samples from the site of disease identifies gene signatures that can reliably distinguish tuberculosis from sarcoidosis using computational classification tools. Our data highlight the superior discriminatory power of multiple gene expression differences over a single marker in complex disease and generate a pathway for biomarker discovery in the management of tuberculosis and sarcoidosis.

S37 MATRIX METALLOPROTEINASES DRIVE COLLAGEN DEGRADATION AND LEUKOCYTE MIGRATION IN HUMAN TUBERCULOSIS: CLINICAL AND CELLULAR STUDIES

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Introduction and Objectives Tuberculosis (TB) causes disease worldwide and multi-drug resistance is rising. Matrix metalloproteinases (MMPs) cause immunopathological lung matrix destruction, which results in transmission, morbidity and mortality. We specifically investigated collagenases in TB, studying secreted MMP-1 and MMP-8, and membrane bound MMP-14.

Methods Plasma was prospectively collected from TB patients (n = 151), respiratory symptomatics (n = 109) and controls (n = 120). Plasma MMP concentrations were measured by Luminex bead array. Induced sputum MMP-14 mRNA from TB patients and controls was quantified by RT-PCR. MMP-14 expression in TB patient biopsies was studied by immunohistochemistry. Human monocytes were stimulated with Mycobacterium tuberculosis (Mtb) H37Rv or Conditioned Media from Mtb infected monocytes (CoMTb) and MMP-14 measured using flow cytometry. Fluorescent microscopy detected MMP-14 and monocyte driven fluorescent collagen degradation. Monocyte migration was measured by the agarose spot assay.

Results Plasma MMP-1 was elevated in TB (median 229pcg/ml) compared to controls (median 2pcg/ml; p<0.001). MMP-8 was increased in TB (median 8359pcg/ml) compared to both respiratory symptomatics (median 3547pcg/ml; p<0.001) and controls (median 3236pcg/ml; p<0.001), and discriminated TB from respiratory symptomatics with moderate predictive ability, with an area under the curve of 0.79 by receiver operating characteristic analysis. In induced sputum, MMP-14 mRNA (normalised to -actin) was increased 3.3-fold in TB compared to controls (p<0.05) and mRNA levels positively correlated with the extent of lung infiltration on chest radiograph (r = 0.483; p<0.05). Macrophages of TB granulomas in patient biopsies stained strongly positive for MMP-14. Mtb increased monocyte MMP-14 surface expression 31.7-fold (p<0.05) and CoMTb 17.5-fold (p<0.01), secondary to increased mRNA. Mtb-infected monocytes degraded collagen, with co-localised MMP-14 surface expression. Monocytes migrated to the edge of CoMTb-impregnated agarose drops, expressing MMP-14 on migration. Inhibition of MMP-14 activity with a neutralising antibody, decreased Mtb driven collagen degradation by 73% (p< 0.001) and CoMTb driven monocyte migration by 44% (p<0.001). Inhibition of chemokine signalling using pertussis toxin reduced CoMTb driven MMP-14 surface expression by 35% (p<0.05).

Discussion Collagen destruction is critical to pathogenesis in pulmonary TB, and these data implicate three collagenases, MMP-1, -8 and -14, in causing immunopathology and regulating leukocyte migration. MMPs may represent novel diagnostic and therapeutic targets.

Corrections

S Lourenco. S35: MIF-CXCR4 as a novel axis for mesenchymal stem cells recruitment to tumours in vivo. *Thorax* 2013;63(Supp 3):A20. doi: 10.1136/thoraxjnl-2013-204457.42

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