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Nodular rheumatoid arthritis (RA): A distinct disease subtype, initiated by cadmium inhalation inducing pulmonary nodule formation and subsequent RA–associated autoantibody generation

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ABSTRACT

Nodular rheumatoid arthritis (RA) patients have raised rheumatoid factor (RF) and anti–citrullinated protein antibody (ACPA) levels, and are more likely to smoke than RA patients without nodules. Subcutaneous and pulmonary rheumatoid nodules (granulomas) frequently co–exist. Pulmonary rheumatoid nodules develop prior to RA development and have the immunological machinery to generate RF and ACPAs. Pulmonary granulomas have been observed in animal models exposed to cadmium (Cd) inhalation. Cigarette smoke increases pulmonary Cd exposure. It has been suggested that dust and cigarette smoke co–exposure increases localised pulmonary Cd adsorption. We hypothesise that subcutaneous nodular RA represents a distinct disease subtype induced by pulmonary rheumatoid nodule formation and the generation of high levels of RA associated autoantibodies initiated by Cd inhalation via cigarette smoke.

Cohorts of RA patients attending rheumatology clinics in Cornwall, UK (total n = 504) were studied to determine the prevalence of nodular RA, with matched analysis (age, gender and social class) to compare urinary Cd, RF and ACPA levels stratifying for nodular disease and smoking.

In cohort 1 45/303 (14.9%) of the RA patients under regular follow up had nodular disease. Of the RA smokers, 30/155 (19%) were nodular and of the RA non–smokers 15/148 (10%) were nodular. Smoking was significantly associated with nodular RA, odds ratio (OR) = 2.48 95% confidence interval (CI) 1.26–4.88, p = 0.008. Raised urinary Cd levels were significantly associated with nodular RA in non–dust exposed individuals, OR 2.26 (95% CI 1.08–4.73), p = 0.03 compared to dust exposed individuals, OR 0.78 (95% CI 0.35–1.76), p = 0.557, despite fewer pack years (py) at diagnosis (16 vs 20 py). Nodular RA smokers had significantly raised RF levels compared to RA smokers without nodular disease (median RF 171.5 (interquartile range (IQR) 48–394) vs median RF 31.7 (IQR 10.3–170.3), p < 0.00001). RF positivity was significantly more prevalent in nodular RA smokers compared to RA smokers without nodular disease (84/89 (94%) vs. 141/199 (71%), OR = 6.9 (95% CI 2.66–17.91), p < 0.00001). ACPA levels were also significantly raised in nodular smokers compared to non–nodular smokers (median ACPA 250 (IQR 145–426) vs 116 (1–257.5), p < 0.00001), as were ACPA positivity rates (83/89 (93%) vs 123/191 (64%), OR = 7.65 (95% CI 3.17–18.4), p < 0.0001).

These pilot results support the hypothesis that nodular RA represents a distinct disease subtype initiated by cadmium inhalation, which we suggest induces pulmonary rheumatoid nodule formation and generation of RA–associated autoantibodies.

Introduction

Rheumatoid arthritis (RA) is a relatively contemporary disease having been first described in early 19th century Paris [1]. Florid classical RA is a characteristic disease with the development of ulnar deviation, swan neck deformities and subcutaneous nodules [2]. However, even in untreated disease, these features do not always develop, suggesting distinct RA subtypes. Classical features of RA strongly associate with erosive disease [3] which has not been observed in extensive studies of European skeletal remains prior to the 19th century [4], suggesting that classical RA is triggered by a set of relatively contemporary environmental risk factors. Cigarette smoking is the most important identified environmental risk factor for seropositive RA development and accounts for a third of cases [5], associating with erosive and nodular disease when compared to RA without these classical features [6]. However, the association between smoking and subcutaneous nodular RA appears to be dependent on rheumatoid factor (RF) positivity [7].

Rheumatoid nodules are pathognomonic for RA. The presence of rheumatoid nodules previously formed part of the 1987 classification criteria for RA [8]. This is not altogether surprising given that in the 1960s nodules occurred in 30% of RA patients (n = 516) in the UK [9].

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Over time the prevalence of nodules in RA in the UK (1991–1993) has declined to 6% with established disease of 3 years duration [10]. Consequently rheumatoid nodules are no longer included in the updated 2010 classification criteria for RA [11].

Rheumatoid nodules can either be located subcutaneously and are usually apparent over the extensor surfaces of the elbow, over the dorsum of the hand and fingers [2] or develop in the lung and are referred to as pulmonary rheumatoid nodules [12]. Pulmonary rheumatoid nodules were initially thought to be rare in RA as a case series of RA patients (n = 253) failed to identify a single case [13], however, in retrospect, chest X–rays have a marked insensitivity with regards to identifying such nodules. Subsequently, computed tomography (CT) imaging has identified a relatively high prevalence of pulmonary rheumatoid nodules (22–30%) in a number of RA case series [14–17].

There is a striking association between cigarette smoking and the development of pulmonary rheumatoid nodules. Walker [9] observed a high rate of smoking in RA patients with pleural effusion (pleural effusion is recognised to be one of the sequelae of pulmonary rheumatoid nodules). Seventy six per cent of the RA patients studied with pleural effusion were smokers compared to 55% of the total RA cohort studied. Subcutaneous nodules appeared to be associated with the development of pulmonary rheumatoid nodules as the pleural effusion cohort had an increased prevalence of subcutaneous nodules of 10/19 (53%) compared to the prevalence of subcutaneous nodule in the RA population without a pleural effusion 146/497 (29%). Interestingly it was observed that RA associated pleural effusion on occasions preceded the development of RA or presented simultaneously with RA [9].

Prior to this description of a high prevalence of subcutaneous nodules in association with pleural effusions in a non–mining RA cohort in Northern England [9], Caplan described pulmonary nodules in Welsh coal miners [18]. In stark contrast to subcutaneous rheumatoid nodules, it was apparent that pulmonary rheumatoid nodules occurred frequently without RA as a study of miners with pulmonary rheumatoid nodules observed that 82/168 (49%) did not have RA. Furthermore of these men, 71 were tested for the then contemporaneous RA latex test and 25 (34%) were positive. This compares to 0/32 control miners with no lung disease or simple pneumoconiosis [19]. Caplan observed the same phenomenon as Walker in that pulmonary rheumatoid nodules often preceded the development of RA [18]. Unsurprisingly coal mining has been observed to increase the risk of male RA with an odds ratio of 8.47 (95% CI 2.59 to 27.66) [20]. The prevalence of smoking was high in miners with pulmonary rheumatoid nodules; a study of lung function observed that 18/23 (78%) of miners with a documented smoking history were current smokers [21].

These historic studies are of contemporary relevance as it has been suggested that RA can be initiated in the lung via local RA associated autoantibody generation [reviewed in [21]]. A highly relevant, important observation of the nature of pulmonary rheumatoid nodules has been made by Highton et al [23]. Pulmonary rheumatoid nodules have the immunological “machinery” to generate RA associated autoantibodies, evidenced by the presence of B lymphocytes and ectopic lymphoid follicles [23]. Such histological changes have not been observed in subcutaneous rheumatoid nodules [24].

It has been suggested that cadmium (Cd) exposure may be implicated in the pathogenesis of seropositive RA as Cd associates with cigarette smoking, social deprivation, living within 30 m of a main road, residency in certain geographical locations of the United States of America and a plethora of occupations associated with RA development [25]. This hypothesis is specifically relevant to pulmonary rheumatoid nodule (granuloma) formation as a number of animal studies have observed that Cd nanoparticles nebulised into the lung can initiate the development of pulmonary nodules [26–28]. Cigarette smoking is strongly associated with an increased lifelong exposure to Cd and this is reflected in raised urinary Cd levels [29]. Median, gender specific UK levels for urinary Cd have been determined [30].

However, the relationship between measurable bodily Cd levels and disease is complex. For example, chronic obstructive pulmonary disease (COPD) is associated with raised lung tissue levels of Cd, but not necessarily raised urinary Cd levels [31]. As COPD is more strongly associated with co–exposures to both inhaled dust and cigarette smoke rather than either alone [32] we have suggested that lung Cd adsorption by the inhaled dust results in highly localised lung Cd levels and triggers disease [33]. As we hypothesise that enhanced adsorption of Cd onto intra–pulmonary inhaled substrates will stimulate granulomatous nodule formation, this may result in a reduced systemic absorption and therefore reduced blood and urinary level of Cd despite high local lung levels. Given that dust inhalation is common in RA populations [34], it is essential that the occupational history in relation to dust exposure is accounted for when considering urinary Cd levels as a marker of Cd exposure.

Accordingly, we hypothesised that RA nodular disease represents a distinct subset of RA with elevated RF, ACPA and appreciably raised urinary Cd levels (> 95th centile as determined for UK populations) specifically in those RA patients unexposed to occupational dust exposure.

Methods

Subjects

Two cohorts of RA patients were studied. Cohort 1 (n = 303) consisted of all RA males and females attending routine rheumatology clinics at the Royal Cornwall Hospital, Cornwall, UK from August 2017 to February 2018 to determine prevalence of nodular RA, as part of Departmental Audit. Cohort 2 consisted of prospectively gathered nodular RA males and females (n = 92), matched for age (+/– 2 years), sex, and smoking history (+/–2 pack years), to patients previously collected as part of project IRAS ID 194833, approved by South West Regional Ethical Committee (UK) as previously described [34] (n = 133). Specifically more males were recruited to this arm of the study as our unit were actively investigating the relationship between occupational exposures and the development of male RA. Cohort 2 (n = 225) was stratified for nodular disease and smoking with comparison made for urinary cadmium. 3 cases were excluded as extreme outliers with cutoff value of > 3 μmol/mol creatinine used to bias towards the null hypothesis.

Both cohorts were amalgamated (Cohort 3) with duplicate records excluded (n = 24). RF and ACPA levels were compared between all RA patients (n = 504) stratified for nodular disease and smoking.

18 patients were excluded from ACPA analysis due to incomplete data (n = 6 RF negative, n = 3 RF weak positive, n = 9 RF strong positive), Fig. 1.

Data was anonymised at source. Age, age of RA onset, disease duration, smoking history prior to disease development, RF levels at disease onset and subsequent ACPA levels were recorded as part of routine clinical practice. Patient occupational histories were recorded as part of ongoing clinical audit using methodology previously described [34]. All patients fulfilled 2010 ACR/EULAR RA criteria at diagnosis [11], Table 1.

Autoantibody measurement

RF was measured with Tina–quant Rheumatoid Factors II Test System (Roche Diagnostics Corporation), with a value of < 14 IU/mL considered as negative as per manufacturer guidelines. ACPA was measured by Second Generation E170 Anti–CCP analysis (Roche Modular Analytics), with a negative value of < 17 U/mL as per manufacturer guidelines.

Social deprivation analysis

Social deprivation analysis was undertaken through the UK

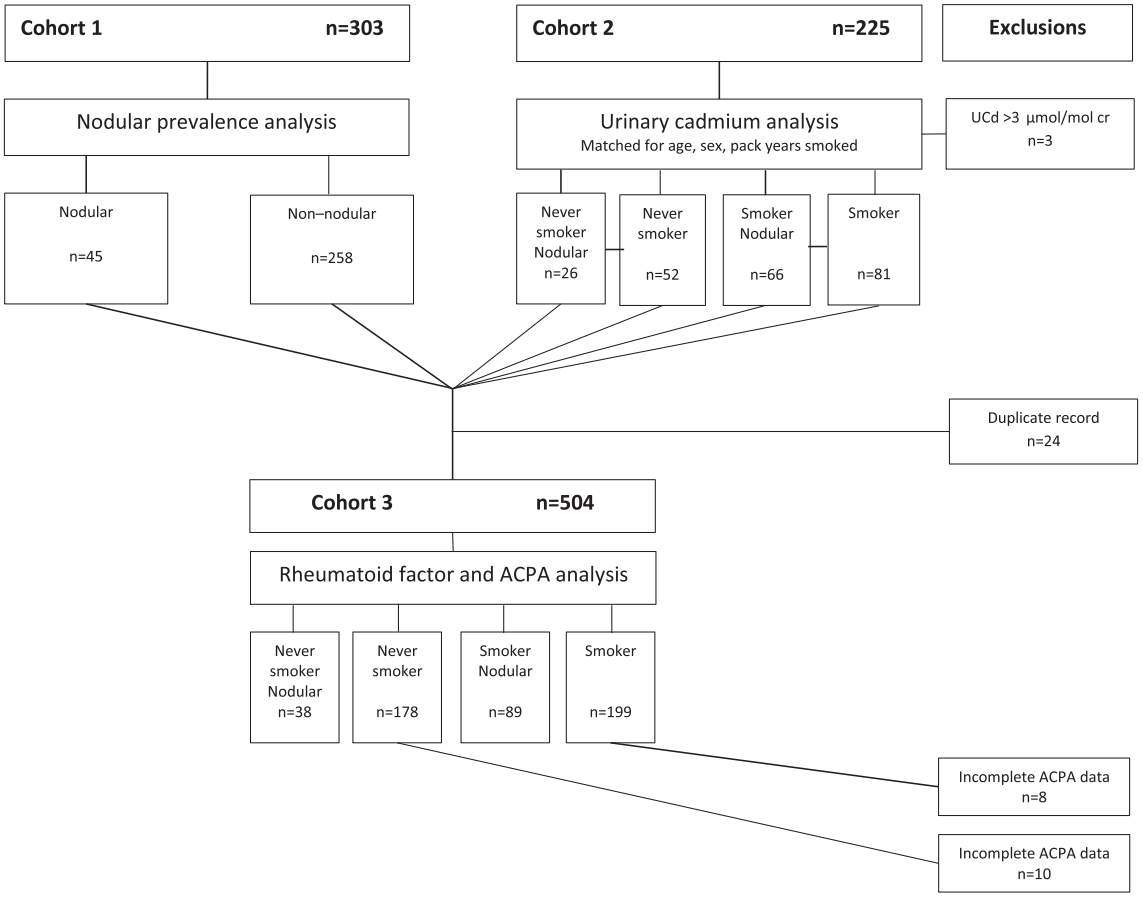

Fig. 1. Flow diagram of patients included for analysis with reasons for exclusion.

government validated Index of Multiple Deprivation (IMD), a deprivation rank score of 32 844 neighbourhoods weighted by income, health/disability, education, housing/service access, crime and living environment, converted to equal deciles [35].

Statistical analysis

Chi square tests and multivariate logistic regression analysis was used to examine relationships between smoking, nodularity and urinary Cd levels, adjusted for gender. The Mann–Whitney *U* test was used for non–parametric comparisons of continuous data of differing sample group sizes, with values are expressed as a median (IQR) or number (%). All data were analysed using commercially available software (Microsoft Excel (Microsoft Corp) and Number Cruncher Statistical System for Windows (NCSS60)).

Urinary cadmium analysis

Patients supplied first pass morning mid–stream urine samples into 13 ml sterile polystyrene urine sample tubes (Thermo–Fisher, Newport, UK). Samples were posted within 72 h to the Supra–Regional Assay Service Trace Elements Laboratory, Guildford, Surrey. Urinary cadmium was analysed by inductively coupled plasma mass spectrometry (ICP–MS), using a fully validated method previously described [30]. An appreciably raised urinary Cd was defined as a urinary Cd level above the 95th centile as determined for UK populations unexposed to occupational Cd, equating to 0.65 mmol/mol creatinine (females), and 0.42 mmol/mol creatinine (males). The median levels were reported as 0.19 mmol/mol creatinine and 0.16 mmol/mol creatinine respectively for females and males [30].

Table 1
Demographic data for each cohort.

	Cohort 1 n = 303	Cohort 2n = 225	Cohort 3n = 504
Age at diagnosis (years, median (IQR))	54 (43–63)	54 (45–61)	54 (44–63)
Male sex (%)	99/303 (32.7%)	129/225 (57.3%)	221/504 (43.8%)
Female sex (%)	204/303 (67.3%)	96/225 (42.7%)	283/504 (56.2%)
Disease duration (years)	9 (3–16)	11.5 (6–22)	10 (4–18)
Median RF at diagnosis (IQR)	38.4 (1–169.5)	70.4 (19.4–215.1)	51 (14.9–181.5)
Prevalence RF + (%)	219/303 (72.2%)	184/225 (81.8%)	381/504 (75.6%)
Median ACPA at diagnosis (IQR)	161 (1–260)**	186.5 (25.6–366.5)	180 (1–319.8)
Prevalence ACPA + (%)	211/285 (74.0%)**	176/225 (78.2%)	349/486 (71.8%)
Smoking prevalence: smoker or ex–smoker (< 20 years) at diagnosis	151/303 (49.8%)	147/225 (65.3%)	288/504 (57.1%)
Median pack years smoked (IQR)	30 (15–40)	11 (0–26)	17(0–27.8)

*Removed from combined cohort as record duplicated n = 24.
** Incomplete ACPA data (RF– n = 6, RF weak + n = 3, RF strong + n = 9).

Smoking history

Pack years smoked was recorded prior to the diagnosis of RA. One pack year is deemed equivalent to smoking 20 cigarettes daily for a year. A smoker was defined as an individual that had smoked in a period up to 20 years before RA diagnosis and > 5 pack years total. A non–smoker was defined as an individual who had either never smoked or had smoked in the distant past (> 20 years prior to the diagnosis of RA) and < 5 pack years total.

Chest X-rays

All the RA patients had chest x-rays undertaken as part of their routine clinical management. No patients were reported to have pulmonary rheumatoid nodules.

Subcutaneous rheumatoid nodules

Individuals were examined in clinic to determine the presence of characteristic rheumatoid nodules on the hands, forearm, elbow and feet. Patients who had undergone surgical removal of nodules and histological examination had confirmed the diagnosis, were considered to be a rheumatoid nodular patient irrespective of the presence of rheumatoid nodularity at the time of the examination. No radiological evidence of pulmonary rheumatoid nodules was collected.

Results

Demographics

The median age, age of RA onset, disease duration, smoking history prior to disease development, RF levels at disease onset and subsequent ACPA levels are recorded in Table 1 for cohorts 1–3. There was an increased prevalence of males in cohort 2 as a result of our particular interest in risk factors associated with male RA development [34]. The prevalence data in cohort 1 in terms of age and gender are broadly in line with other UK RA populations [3].

Risk factors for rheumatoid nodularity (cohort 2)

Current smoking was significantly associated with rheumatoid nodules (OR 2.74 (CI 1.29–4.72)), p = 0.006. Former smokers were not at an increased risk of rheumatoid nodules, OR 1.14 (CI 0.56–2.28). However, when accounting for pack years smoked the principal association was between pack years smoked and rheumatoid nodularity (data not shown).

Dust exposure alone was not associated with rheumatoid nodularity, OR 1.11 (CI 0.64–1.94) when corrected for pack years smoked (data not shown).

Gender and Cd levels

Both males and females displayed higher median Cd levels than unexposed, non–disease UK median data [30]. In men (n = 128) the median Cd levels were 0.38 (IQR 0.16–0.42) and in women (n = 95) the median Cd levels were 0.57 (IQR 0.19–0.65), p < 0.00001.

Nodularity, gender and Cd levels

Overall, nodular RA patients (n = 92) had median Cd levels of 0.54 (IQR 0.31–0.82) mmol/mol creatinine compared to non–nodular (n = 131) RA patients of 0.43 (IQR 0.28–0.67) mmol/mol creatinine with no significant difference (p = 0.13) in median Cd levels observed.

In female nodular RA (n = 38) the median Cd level was 0.64 (IQR 0.43–0.91) compared to a median Cd level of 0.5 (IQR 0.35–0.74) mmol/mol creatinine in female non–nodular RA (n = 57), p = 0.06, Fig. 2. In contrast, in male nodular RA (n = 54) the median Cd level of 0.385 (IQR 0.25–0.68) mmol/mol creatinine was very similar to the Cd levels of 0.37 (IQR 0.26–0.57) mmol/mol creatinine in non–nodular male RA (n = 74), p = 0.6, Fig. 2.

Subsequent analysis of occupations as previously described [34] revealed that the majority of the men (90/128, 70.3%) were dust exposed. Given that very few females had such exposures (8/95, 8.4%), we analysed Cd levels in relation to dust exposure and the risk of rheumatoid nodularity given that female nodular patients had the highest Cd levels of any group studied (almost twice as high as male nodular smoking RA patients).

In non–dust exposed individuals an appreciably raised Cd level was significantly associated with nodular RA, OR 2.26 (95% CI 1.08–4.73), p = 0.03. In dust exposed individuals an appreciably raised Cd level was not associated with nodular RA, OR 0.78 (95% CI 0.35–1.76), p = 0.557.

In non–smoking, non–nodular patients 1/19 (5.26%) had appreciably raised Cd levels compared to 3/10 (30%) of the non–smoker nodular patients. Amongst smoking non–nodular patients 39/79 (50.6%) had appreciably raised Cd levels compared to smoking nodular patients 36/67 (46%).

Nodularity and RA–associated autoantibodies

Nodular RA smokers had significantly raised RF levels of compared to RA smokers without nodular disease (median RF 171.5 (IQR 48–394) vs median RF 31.7 (10.3–170.3), p < 0.00001), Fig. 3.

RF positivity was significantly more prevalent in nodular RA smokers compared to RA smokers without nodular disease (84/89 (94%) vs. 141/199 (71%), OR = 6.9 (2.66–17.91), p < 0.00001).

ACPA levels were also significantly raised in nodular smokers compared to non–nodular smokers (median ACPA 250 (IQR 145–426) vs 116 (1–257.5), p < 0.0001) as were ACPA positivity rates (83/89 (93%) vs 123/191 (64%), OR = 7.65 (3.17–18.4), p < 0.0001), Fig. 4.

RF levels were significantly elevated in nodular never smokers, median RF 118 (62.6–267.3) vs. 30.5 (7–95.3) for never smokers without nodular disease, p < 0.00001, Fig. 3. ACPA levels were similarly significantly higher in nodular never smokers, median ACPA 245 (69.3–385.1) vs. 147.5 (1–280.3) for never smokers without nodular disease, p = 0.02, Fig. 4.

No significant differences were observed in RF (p = 0.25), or ACPA (p = 0.67) between nodular never smokers and nodular smokers.

Discussion

Nodular RA environmental exposures

Rheumatoid nodules have been of great interest to rheumatology researchers for over a hundred years. Histologically, rheumatoid nodules are granulomas consisting of a fibrous tissue shell arranged around a centre of fibrinoid necrosis [36]. Granulomas have been reported to occur in individuals in association with a number of metals including aluminium, barium, beryllium, cobalt, gold, titanium and zirconium [37]. In addition, Cd has also been observed to induce the formation of granulomas when nebulised into the lung in animal models [26–28]. Autophagy has emerged as an important process by which antigen presenting cells generate and present citrullinated proteins/peptides [38]. This process is induced in vivo by Cd and zinc rather than other metals such as cobalt, iron, lead, mercury and selenium [39]. Given that Cd as opposed to zinc is significantly raised in smokers as opposed to never smokers [40] and the strong relationship between smoking and rheumatoid nodules as highlighted above, we have hypothesised that Cd exposure is associated with nodular RA.

In this study we observed that an appreciably raised urinary Cd level in non–dust exposed RA patients was significantly associated with the presence of peripheral rheumatoid nodules. We suggest that inhaled Cd

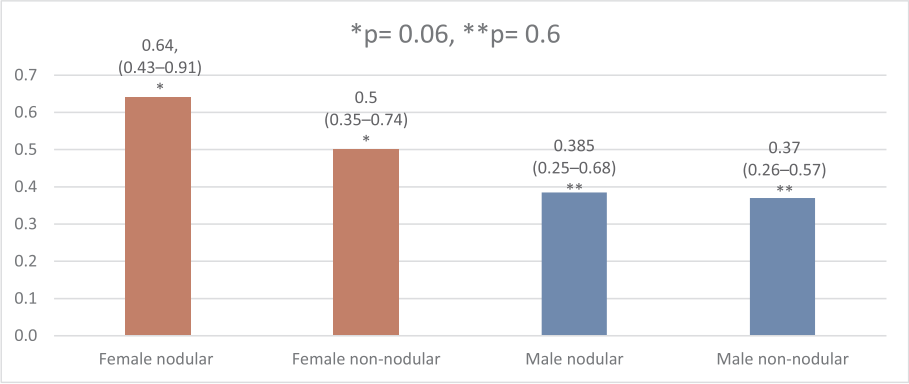

Fig. 2. Significantly elevated urinary cadmium (mmol/mol creatinine) in female nodular patients, but not in males *p = 0.06, **p = 0.6.

and the subsequent accumulation of this metal in the lung triggers a granulomatous lung reaction as has been described with other inhaled metals such as beryllium [41]. As there is a striking concordance between pulmonary and peripheral rheumatoid nodule formation we suggest that smoking induces rheumatoid peripheral nodules as a consequence of Cd exposure.

Peripheral and pulmonary nodule differences

The central area of the rheumatoid nodule is necrotic and contains fibrinogen and in the peripheral part of the necrotic area is fibronectin [42]. Citrullination is noted to occur within the rheumatoid nodule as a study noted positive citrulline staining in the majority of 26 cases (70%) [43]. At the junction of the necrotic centre and the outer fibrous shell is a palisade of activated macrophages and fibroblasts. In the outer layer clustered around blood vessels are T lymphocytes of both CD4 and CD8 subtype and these tend to accumulate around vessels in the area immediately outside the palisade. In close proximity to T cells, dendritic cells have been observed [42]. Therefore there is the potential for antigen presentation in the peripheral nodule. However, peripheral rheumatoid nodules lack of organised lymphoid tissue containing plasma cells. Despite the abundance of citrullinated antigens such as fibrin and fibronectin, autoantibody generation within the peripheral rheumatoid nodule does not appear to be feasible primarily for this reason.

In distinct contrast pulmonary rheumatoid nodules have been observed to consist of lymphoid aggregates containing both B lymphocytes and T lymphocytes and germinal centres containing follicular dendritic cells in addition to the typical histological findings of the peripheral rheumatoid nodule [23]. Supporting the hypothesis that pulmonary nodules generate RA autoantibodies to trigger RA development (rather than arise as a result of RF and ACPA generated by the peripheral RA disease process), is the finding by Caplan [18] that pulmonary rheumatoid nodules often preceded the development of RA and occurred commonly in the absence of RF prior to the development of RA [19]. The appearance of pulmonary rheumatoid nodules in the miners described by Caplan appears to be the strongest risk factor ever described in the literature for RA development with an approximate 364–fold increased risk (51% developing RA as compared to a prevalence of RA in the same era in males living in non–mining communities of 0.14%) [44].

How this hypothesis changes understanding on the pathophysiology of nodular RA

Current dogma suggests that rheumatoid nodules develop as a result of the RA disease process generating RF and ACPA, and that immune complexes deposit in the subcutaneous tissues possibly enhanced by local pressure point areas at the elbow, facilitating a local inflammatory process with macrophage activation [reviewed in 24]. There has been great interest in the understanding of peripheral rheumatoid nodule formation as it has been suggested that the disease process that occurs in the rheumatoid nodule shares great similarities with the inflammatory process in the synovial tissue described in RA [45].

We have hypothesised that pulmonary rheumatoid nodules generate RA associated autoantibodies. In this study we observed that nodular RA patients had markedly elevated levels of RA autoantibodies compared to non–nodular RA patients and this remained the case when nodular patients were stratified for smoking. Smoking is the most important environmental risk factor for the development of raised RF levels in RA and is related to pack years smoked [46]. However the pack years smoked were very similar between smoking nodular and non–nodular RA patients and therefore do not explain the marked difference reported here. Remarkably non–nodular RA smokers had very similar

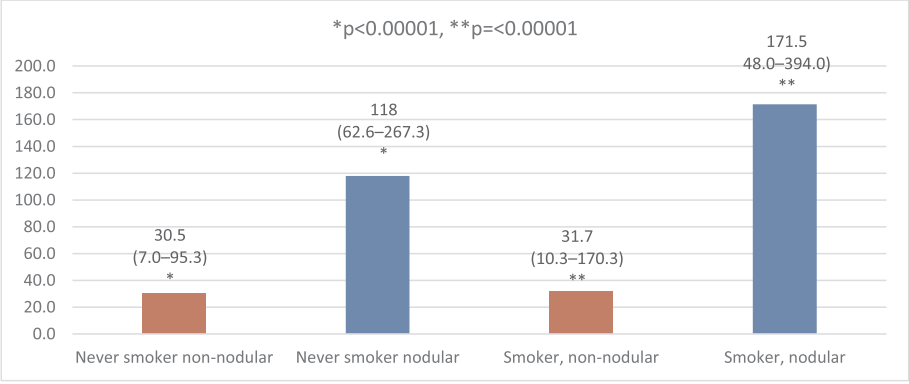

Fig. 3. Significantly elevated median RF (IQR) levels in nodular RA smokers and non–smokers *p < 0.00001, **p= < 0.00001.

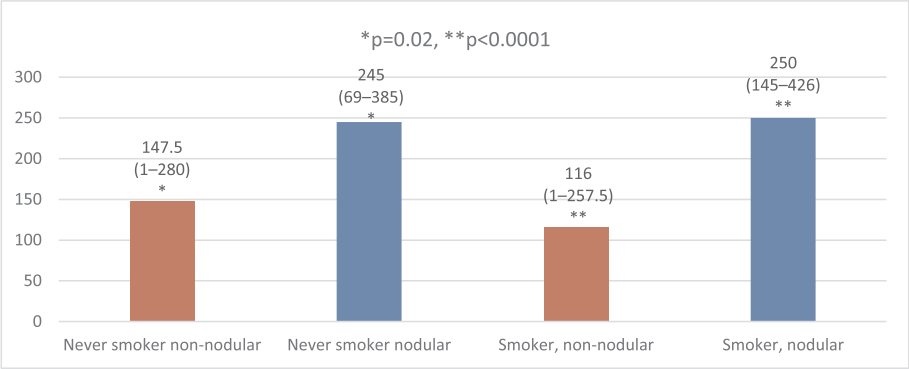

Fig. 4. Significantly elevated median ACPA (IQR) levels in nodular RA smokers and non–smokers *p = 0.02, **p < 0.0001.

RF levels to RA non–smokers without nodules. This finding is the first to be reported in the literature and suggests that smoking per se does not increase RF levels. We hypothesise that smoking may generate pulmonary rheumatoid nodule formation which in turn generate the rheumatoid associated autoantibodies and the subsequent development of peripheral rheumatoid nodules.

Limitations

A limitation of this study was to use the presence of peripheral rheumatoid nodules as a surrogate for the presence of pulmonary rheumatoid nodules. It is conceivable that in some patients with peripheral rheumatoid nodules that the nodules developed as a result of RA associated autoantibody production in the joint as a result of long-standing RA.

The relationship between measurable bodily Cd levels and RA is complicated. For example we have recently demonstrated a markedly increased prevalence of inhalational occupational exposures in 546/726 (75%) men with RA [34]. These exposures included potent Cd adsorbers such as kaolin, silica, bitumen tar and wood dust. Furthermore we have suggested that lung Cd adsorption by the inhaled dust results in high lung levels and triggers disease [33]. Accordingly an enhanced Cd lung adsorption will result in a reduced systemic absorption and therefore reduced urinary level of Cd despite high lung levels which would enhance the risk of pulmonary rheumatoid nodule formation. Urinary Cd levels can also be influenced by diet and iron deficiency anaemia [29], however there is no medical literature to support a relationship between dietary intake and/or iron deficiency, and nodular RA.

Interestingly in this study we found that urinary Cd levels were significantly lower in dust exposed nodular RA patients compared to non–dust exposed nodular and non–nodular RA patients. This highlights the importance of lung Cd adsorption and possibly suggests that measuring bodily Cd levels in terms of urine or blood levels may overlook high levels of Cd in the lung which may have the potential to initiate RA via the generation of rheumatoid nodule formation. We suggest that studies investigating the relationship between RA pathogenesis and Cd levels take into account the occupational history as well as the smoking history of the patient as blood or urine levels in Cd exposed individuals are likely to be reduced as a result Cd adsorption in co–exposed lungs. This is particularly relevant to men with RA as the majority of these individuals have been exposed to occupational dusts [34]. It is noteworthy that a large Korean epidemiological study of RA prevalence revealed a strong association between Cd blood levels in women, but not men [47].

Conclusions

There does appear to have been a change in the natural history of RA over the last 40–50 years in terms of expression of nodular disease. It would be easy to ascribe this change to better treatment strategies and more efficacious medications for RA. However, these changes would not affect the type of RA at presentation. For example a study of 102 early RA patients in London, UK in the mid– 1970 s observed that 12/102 (12%) individuals had subcutaneous nodules at presentation rising to 32/102 (31%) at 3 years [48]. In contrast a study in Norfolk, UK (1990–1993) observed that 37/486 (7.6%) of RA patients had subcutaneous nodules at presentation and at 3 years follow up this had fallen to 31/486 (6.4%) [10]. This stark change appears to have occurred before the advent of biologics therapies and before the routine first line use of methotrexate. We suggest that the natural history of nodular RA may reflect the marked drop in Cd exposure in UK society. The industrial revolution was associated with a 15–fold increase in anthropogenic emissions of Cd in Western Europe [49] and since the 1960 s there has been a 2.5–fold decrease in emissions of Cd [50]. Additionally the marked reduction in the prevalence of smoking is also likely to reduced individuals exposure to Cd [51]. This is not the first study to observe an association between raised bodily Cd levels [47,52–54], however this study is the first to describe a particular RA phenotype that most strongly associates with an increased Cd exposure. Additionally, this hypothesis has generated the first evidence of an environmental risk factor, other than cigarette smoking, for the development of nodular RA.

As described above the rheumatoid nodule is a potentially important source of citrullinated proteins such as fibrin and fibronectin which can be presented to the immune system by resident antigen presenting cells such as macrophages, fibroblasts and dendritic cells. Pulmonary rheumatoid nodules also have the potential to generate RA associated autoantibodies. Given that a recent study observed intracellular citrullination of proteins in lung cells exposed to Cd [55], we hypothesise that Cd inhalation orchestrates the development of pulmonary rheumatoid nodules, intracellular citrullination and the subsequent formation of RA associated autoantibodies leads to immune complex formation and activation of various immune cells that trigger the development of nodular RA. However, Cd exposure may also predispose to non–nodular RA. In this study we noted appreciably raised Cd levels in non–nodular patients irrespective of their smoking history and it is conceivable that Cd accumulation in the bone marrow may result in altered mesenchymal stem cell viability as described in an animal model [56]. Certainly mesenchymal stem cells have the potential to have a significant role in the pathogenesis of RA [57].

It is noteworthy that 27 years ago that Fischer in *Medical hypotheses* hypothesised that tobacco smoking was a risk factor for RA [58]. We have extended Fischer's hypothesis further and suggest that specifically, it is Cd derived mainly from cigarette smoke that triggers RA disease development. We suggest that one potential mechanism by which Cd triggers RA is as a result of lung granuloma formation with a subsequent autoantibody response triggering seropositive RA.

This study has made the assumption that RA patients with peripheral nodules are more likely to have pulmonary rheumatoid nodules, however, we have no radiological evidence to support this. A recent study [59] has demonstrated that 73% of patients with CT confirmed pulmonary rheumatoid nodules had peripheral rheumatoid nodules compared to 20% of RA patients with lung tumours with a similar smoking history. Therefore we feel that we have made a reasonable assumption that nodular RA patients may also have pulmonary rheumatoid nodules.

Further studies are required to undertake chest CT scans of RA patients with a similar smoking history and occupational history with or without a history of peripheral nodularity. These studies would help to determine the prevalence of pulmonary nodules in these 2 distinct groups of RA patients and whether pulmonary rheumatoid nodularity correlates with RF titres. Additionally a study could be undertaken to investigate heavy smokers who have been found to have strongly positive RFs and ACPAs who do not have RA and compare their chest CT scans with seronegative heavy smokers without RA.

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Author contributions.

All authors were involved in drafting the manuscript and designing the tables and figures. All authors approved the final version before submission.

Study conception and design.

Acquisition of data.

Analysis and interpretation of data. Hutchinson, Murphy

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2018.10.021.

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