

Rheumatological diseases and cancer: the hidden variable of radiation exposure

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Recently, several different meta-analyses have shown that rheumatological diseases—including systemic sclerosis (SSc), systemic lupus erythematosus, rheumatoid arthritis and psoriatic arthritis—are associated with an increased risk of cancer, in particular non-Hodgkin's lymphoma, lung and liver cancer.^{1–6} Several hypotheses have been advanced to explain this finding, including immune dysregulation, biological therapy and exposure to common environmental risk factors.⁷ These data may suggest the inclusion of medical radiation as a potential, and verifiable, iatrogenic risk linking SSc and cancer. This malignant induction may be potentiated by the concomitant use of drugs, such as methotrexate and cyclophosphamide, or drugs such as paracetamol. In fact, these drugs are known to amplify the genotoxic effects of medical radiation. In addition, in some rheumatic diseases, the exposure to medical radiation is associated with an intrinsic higher vulnerability for DNA instability.

Frauenfelder *et al*⁸ present the prospective validation of a dedicated, 9-slice high resolution computed tomography (HRCT) protocol with reduced radiation dose for the detection of interstitial lung disease in SSc patients. This paper addresses clearly the fact that the dose reduction is becoming today a hot issue in clinics. Herein, we wish to draw the attention of the rheumatological community to the hypothesis that, in rheumatological patients, the use of medical radiation may pose an additional risk for cancer development, possibly potentiated by the concurrent use of antirheumatic drugs.

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MEDICAL RADIATION AS A POTENTIAL CARCINOGEN

Medical radiation is suspected to contribute to the development of cancer. According to the linear no-threshold theory, all radiation poses some risk of cancer induction, although the magnitude of this risk remains unclear, particularly at very low doses. The average background exposure of a US citizen approximates 3.0 milliSievert (mSv, corresponding to the radiological dose equivalence of 150 chest X-rays) per person per year, as estimated in 2006.⁹ Doses of examinations commonly employed in rheumatology patients range from 2 to 8 mSv for a chest CT (100–400 chest X-rays) to 10–40 mSv for a myocardial perfusion scintigraphy (500–4000 chest X-rays).¹⁰ The radiological risk is considered cumulative in nature; thus, each exam using radiation increases the risk. Furthermore, children are more sensitive to radiation than adults, and females are more sensitive to radiation risks than males.¹¹ Rheumatological patients, often young at disease onset and very frequently female, are therefore more prone to radiation related risks. The chronic nature of most rheumatological diseases also renders our patients more vulnerable to experiencing the cumulative effects of multiple and repeated X-ray studies. Although imaging is a fundamental tool in the diagnosis and monitoring of disease evolution and response to therapy,¹² we wish to draw attention to the need of appropriate risk-benefit analysis for the type and frequency of studies.

The available epidemiological evidence linking radiation exposure to increased cancer risk is well established for doses >10–50 mSv, which may be experienced by our patients during one admission, after one episode of care, or in some circumstances a single examination.¹² A recent study of 180 000 people exposed to CT scan in the UK found an increasing risk of leukaemia and brain cancer with increasing radiation exposure, with cumulative ionising radiation doses from three head CTs tripling the risk of brain tumours and 5–10 head CTs tripling the risk of leukaemia.¹³ Among 680 000 Australians exposed to a

CT scan when aged 0–19 years, cancer incidence was increased by 24% compared with the incidence in over 10 million unexposed people.¹⁴ Epidemiological evidence is also emerging showing a link between increased radiation exposure and subsequent increased risk of cancer in adult populations of patients with ischaemic heart disease.¹⁵

In rheumatic patients, imaging of the chest (an anatomic region that includes the radiosensitive organs lung, female breast and bone marrow) is commonly performed.¹⁶ The lungs may experience relatively high organ doses from right heart catheterisation for suspected pulmonary arterial hypertension,¹⁷ and from chest CT employed for detection of lung involvement.¹⁸ Gallium scintigraphy previously often used to assess pulmonary disease activity,¹⁹ and cardiac stress scintigraphy with thallium or technetium-based tracers such as sestamibi to evaluate coronary and myocardial involvement.²⁰ The organ sites where imaging has been performed often correspond to where malignancy has developed. Cumulative radiation contributes to the increase in cancer.²¹ Risk estimates are further complicated, and therefore more subject to being contested because cancer induction often occurs years or decades after exposure.

VULNERABILITY OF RHEUMATOLOGICAL PATIENTS TO DAMAGING EFFECTS OF RADIATION: AGE, GENDER, GENES AND DRUGS

The dose-risk curve in radiation risk is established from large epidemiological data banks, including >100 000 survivors of the atomic bomb, >400 000 nuclear power plant workers and >800 000 patients exposed to diagnostic medical radiation. The challenge ahead is to translate the generic population risk obtained from epidemiological data into a personalised risk. Several genetic and pharmacological variables can affect the variability of damage observed for any given level of radiation. For instance, radiation-induced chromosomal damage is amplified by genetic polymorphisms or gene mutations (such as BRCA1 and BRCA2) of genes involved in DNA repair.²² A similar situation may occur in rheumatological patients in whom epidemiological, genetic and pharmacological factors may enhance vulnerability to a given dose of radiation, making the linear relationship linking risk to dose progressively steeper (figure 1). First, rheumatological patients are much more often women (with a 4:1 ratio), who are 38% more vulnerable to radiation than men.¹¹ Second, the age at first

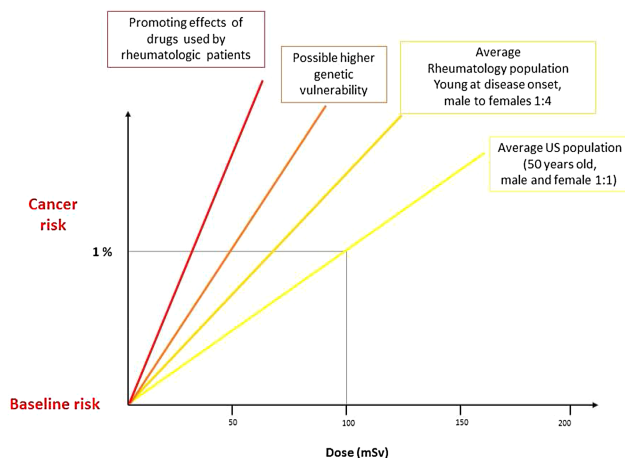


Figure 1 The population risk estimated for an average population is in reality derived from a spectrum of risks, for instance with higher risks being associated with female gender, younger-than-average age, mutation of genes involved in DNA repair and presence of other environmental carcinogens such as alkylating agents or some anti-inflammatory drugs. The 'average' risk of one extra-cancer for every 100 mSv radiation exposure can in this way increase significantly, even detectable with a classic epidemiology approach on a few thousand patients.

diagnosis is on average relatively young, and radiation vulnerability increases with younger age, being twice as high at 30 years than at 50 years of age.¹⁵ Third, data suggest a particular sensitivity of DNA from rheumatology patients, with defective repair ability. *Ex vivo* studies in peripheral blood lymphocytes from children with systemic lupus, juvenile rheumatoid arthritis and SSc show a twofold increase in biomarkers of DNA damage as well as delayed repair of DNA damage after irradiation, suggesting an intrinsic increased vulnerability to effects

of ionising radiation.²³ The increased vulnerability to radiation has also been observed for non-cancer effects evoked by high-dose therapeutic radiation exposures, such as fibrosis after radiotherapy, which may precipitate SSc or cause a generalised worsening of the underlying disease, promoting oxidative stress, hypoxia and microvascular damage.^{24 25} Fourth, rheumatological patients frequently use alkylating agents such as methotrexate and cyclophosphamide that are known biological modifiers of radiation-induced DNA damage,²⁶ which may potentiate

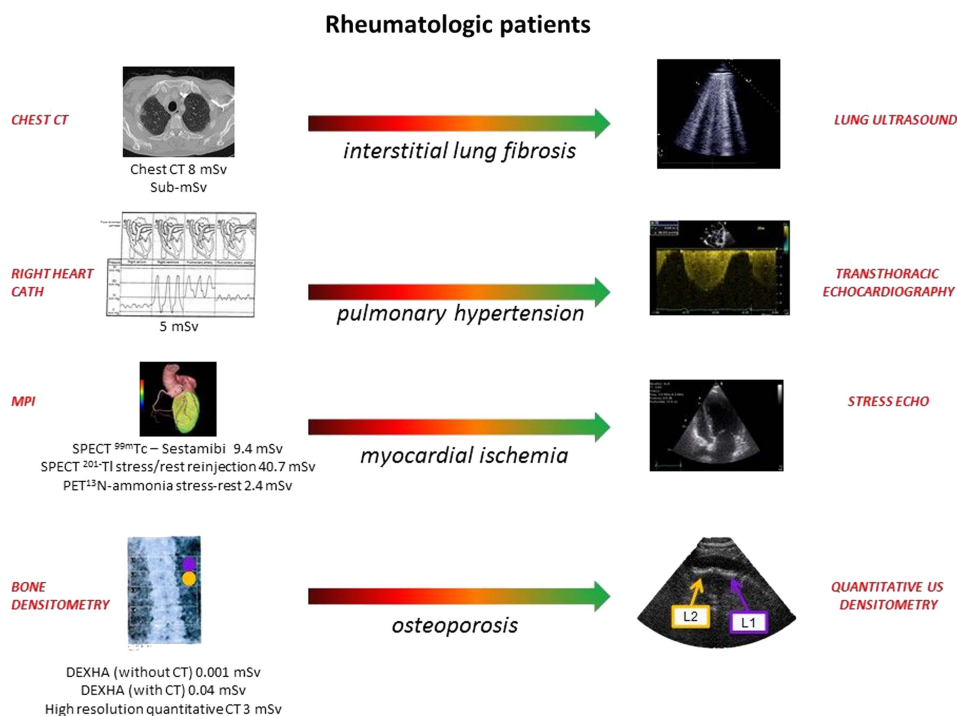
supra-additive genotoxic effects with radiation.^{27 28} In addition, some anti-inflammatory drugs, such as paracetamol, have inhibitory effects on DNA repair in mammalian cells and may contribute to genotoxicity in humans.^{28 29}

TAKE-HOME MESSAGES FOR THE RESEARCHER AND THE CLINICIAN

The radiation to cancer-induction relationship can be prospectively tested with further data mining, including reference doses (when actual delivered doses are not available), genotyping, and characterisation of type and use of concomitant medications, as variables. In practical terms, the issue of radiation risk should stimulate re-evaluation of imaging strategies, moving away from standardised one-size-fits-all screening for disease to symptom-based, patient-centric or tailored strategies emphasising risk-benefit analysis on an individual basis, including justification and optimisation of imaging protocols. In addition, the diagnostic strategy in patients, with SSc for example, might substantially shift towards radiation-sparing approaches whenever possible, taking full advantage of the technological advances of the last 5 years. In SSc, recent studies have shown that screening for interstitial lung disease with a limited number of high resolution CT slices may be sufficient for screening and follow-up.^{8 30}

Usually, for the diagnosis of pulmonary hypertension, right heart catheterisation is mandatory but in practice transthoracic

Figure 2 The diagnostic potential of four commonly faced challenges in rheumatology patients: lung fibrosis, pulmonary hypertension, myocardial ischaemia and bone osteoporosis. For each, the imaging menu includes an ionising (left) and non-ionising (right) option, with inherent differences in complexity, cost and availability. With the ionising approach, the true radiation exposure can vary up to 10-fold compared with the reference dose depending on the technology and technique used: the dose administered should always be known and recorded in patients' records. Reference doses are taken from.^{9 38} Ultrasound osteoporosis image by courtesy of Echo-light and Casciaro S.



resting and exercise stress echocardiography can also rule out this pulmonary complication in SSC³¹ because patients with a normal stress echo are unlikely to develop pulmonary hypertension in the following years.³² Myocardial perfusion scintigraphy is still widely used for diagnosis and prognostic stratification in coronary artery disease, but its utilisation has fallen in recent years due to radiation exposure concerns³³ and the dissemination of alternative, equally accurate radiation-free techniques such as stress MRI and stress echocardiography.^{34 35} Osteoporosis is usually assessed using radiological techniques, but recently quantitative ultrasound densitometric methods have become available.³⁶ Lung fibrosis is ideally tracked with chest CT, but limited section CT can be substituted, and recent research suggests that ultrasound and MRI may be an accurate alternative³⁷ even for early stages of disease, in particular in the follow-up and screening of SSC patients; with the additional benefits that it is a simple, low-cost and portable technique.³⁸ When lack of available technology and expertise do not allow the use of an alternative radiation-free technique, great care should be taken to use the lowest dose radiation methods: for myocardial perfusion imaging, sestamibi is superior to thallium with single-photon emission computed tomography (SPECT), and positron emission tomography (PET) (with rubidium or water) is better than SPECT; for lung fibrosis, low-dose and even sub-mSv CT are now available; for right heart catheterisation, optimised use of fluoroscopy can reduce radiation exposure fivefold; and for osteoporosis, high resolution peripheral quantitative CT-based methods are more accurate with substantially less radiation dose than dual X-ray absorptiometry technique (figure 2).

Because of the numerous sources of variability, there is no clear threshold between acceptable and unacceptable exposures for any given examination, but it is reasonable to postulate that any dose administered that has not been considered carefully with risk-benefit analysis and recorded in the patient's records is unacceptable.³⁹ It is wise for the rheumatologist to be well aware of the typical radiation doses and suspected risks of medical radiation, and to prescribe medical imaging while taking into account the principles of justification and optimisation, considering that 'each patient should get the right imaging exam, at the right time, with the right radiation dose' in order to minimise the risk of iatrogenic cancer development.⁴⁰ A prudent use of radiation

is especially important in paediatric patients, who are particularly vulnerable to radiation damage.⁴¹

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