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Prevalence and management of rheumatoid arthritis in the general population of Greece—the ESORDIG study

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Objective. **To assess the prevalence and management of rheumatoid arthritis (RA) in the general adult population of Greece.**
Methods. **This cross-sectional study was conducted on the total adult population (≥19 yrs old) of seven communities (8547 subjects), and on 2100 out of 5686 randomly selected subjects in two additional communities. The study, based on a standardized questionnaire and clinical evaluation and laboratory investigation when necessary, was carried out by rheumatologists who visited the target population at their homes. Diagnosis of RA was based on the American College of Rheumatology (ACR) 1987 criteria.**
Results. **A total of 8740 subjects participated (response rate 82.1%). RA was diagnosed in 59 individuals. The prevalence of RA was 0.68% (95% CI 0.51–0.85); it was significantly higher in females than males ($P < 0.0005$), and increased significantly with age up to and including the 50–59-yr-old group ($P < 0.002$), and then decreased slightly. On their first medical visit, 19% (95% CI 9.7–30.9) of the RA patients had consulted a rheumatologist, while during the first year after disease onset, 61% (95% CI 48.6–73.4) had done so. Early consultation with a rheumatologist and disease-modifying anti-rheumatic drug (DMARD) combination therapy were negatively associated with ACR functional classes II–IV [adjusted odds ratios 0.18 (95% CI 0.04–0.85) and 0.17 (95% CI 0.04–0.72), respectively].**
Conclusions. **The prevalence of RA in the general adult population of Greece is similar to that in many other European countries; early consultation with a rheumatologist and DMARD combination therapy are associated with a better RA outcome.**

KEY WORDS: Rheumatoid arthritis, Prevalence, Epidemiology, Management, Greece.

Introduction

Rheumatoid arthritis (RA) is a chronic and deforming inflammatory disease that produces remarkable morbidity and disability. Epidemiological studies have shown that the prevalence of RA varies broadly from 0.2 to 1.0% in various European, North American, Asian and Australian populations [1]. Most studies in European countries have suggested a prevalence in adult populations ranging from 0.5 to 1.0% [1–7]. However, some studies, especially those from southern European countries, including Greece, have shown a lower prevalence (0.18–0.34%), which raises important questions about the possible involvement of different environmental and/or genetic factors in the aetiology of RA among various European populations [8–10]. Few population-based studies have assessed the care of RA patients [11–13] and data on the association between care and the outcome of RA in the general population are limited.

This part of the ESORDIG (epidemiological study of the rheumatic diseases in Greece) study aimed at assessing the prevalence and management of RA in the general adult population of Greece.

Methods

Study population and subject evaluation

Details on the ESORDIG study population, subject recruitment and evaluation, as well as on quality control have been reported previously [14]. The ESORDIG study was conducted from March 1966 to April 1999 on the total adult population (aged ≥19 yrs old) of two urban, one suburban and four rural areas located in northern, central and southern mainland Greece (8547 subjects), as well as on 2100 out of 5686 randomly selected adult subjects in one additional rural and one suburban community. In the latter areas, every second and third household from a randomly chosen starting point, respectively, was selected (systematic sampling) (Fig. 1); this was for practical reasons since there were only two investigators available for the suburban and one for the rural area. Sixteen rheumatologists conducted the study by visiting the target population at their homes. Each visit involved an interview with each participant that was based on a standardized questionnaire aimed at obtaining a variety of information on socio-demographic characteristics, medical history, and on a specific standardized

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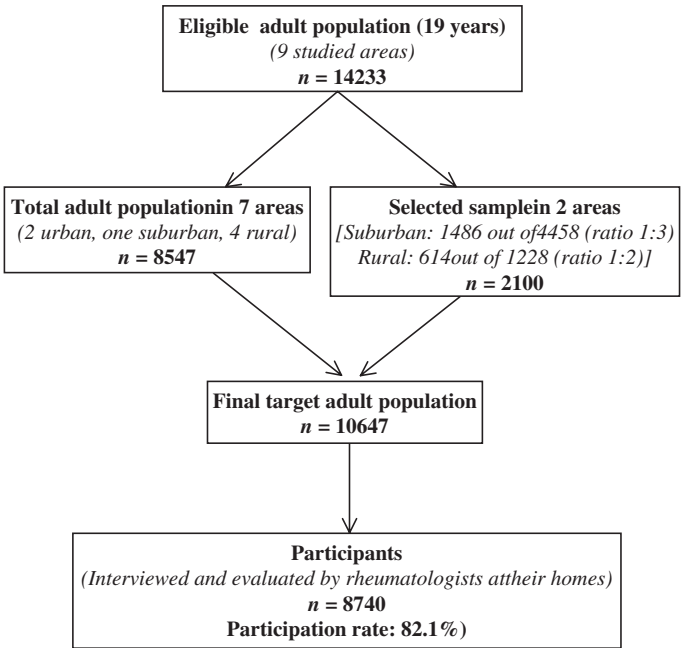

FIG. 1. Flow chart showing the ESORDIG study design.

questionnaire aimed at revealing all subjects suffering from RA. This specific questionnaire was analogous to that used by MacGregor *et al.* [2] and consisted of the following three questions: have you ever had (i) any joint pain, not due to trauma, lasting at least six continuous weeks? (ii) any joint swelling lasting at least six continuous weeks? (iii) morning stiffness in any joint, lasting at least 1 hour before maximal improvement? The sensitivity of this questionnaire to detect cases of RA was shown to be 100% in a pilot study of 45 patients with known RA, performed prior to the start of the ESORDIG study. All subjects who responded positively to any of the three questions of this specific questionnaire were subsequently evaluated by the rheumatologists conducting the study (medical history, clinical examination, assessment of available laboratory and imaging findings), during the same home visit. When necessary, appropriate X-ray investigation and/or other requisite laboratory tests were performed on the following days, and the findings were assessed by the rheumatologists during a second home visit, in order to reach a definite diagnosis. The diagnosis of RA was made on the basis of the American College of Rheumatology (ACR) criteria [15]. Disease remission and functional consequences of RA were assessed using the respective ACR criteria [16, 17].

The effect of non-selection and random selection of suburban and rural populations on the study results was tested in a logistic regression model in which the dependent variable was the diagnosis of RA and the independent variables were the selected/non-selected populations. As previously described [14], data were obtained from a random sample of non-responders on socio-demographic characteristics, past medical history, previous rheumatic disease diagnosis including RA, and the reasons for non-participation in the study.

Protocol approval

The study was conducted according to the declarations of Helsinki and written informed consent was obtained from all the study participants. The protocol was approved by the appropriate committees of the Ministry of Health and the Central Union of Municipalities and Communities of Greece.

Statistical analysis

All analyses were conducted using SPSS v.12.0 for Windows. The chi-square test was used to compare prevalence and percentages, while the comparison of mean values was by Student's *t*-test. Values of $P < 0.05$ were considered significant; 95% confidence intervals (CIs) were given where relevant. A logistic regression model was used for assessing the association of RA with certain factors such as sex, age, marital status, body mass index (BMI), cigarette smoking (pack-yrs), alcohol consumption, level of education, occupation, socioeconomic status and residence in urban, suburban or rural areas. Concerning BMI, cut-off points of $\geq 30\,kg/m^2$ for obesity and $<30\,kg/m^2$ for non-obesity were used [18]. The level of education was defined as low or high on the basis of school attendance up to 9 and >9 yrs, respectively. Multiple logistic regression analysis was also applied for assessing the association of ACR functional classes II–IV with certain factors such as sex, age, residence, BMI, disease duration, disease remission or not, presence of rheumatoid factor or not, early or late consultation with a rheumatologist and disease-modifying anti-rheumatic drug (DMARD) combination therapy.

Results

Of the final target adult population of 10 647 subjects, 8740 participated in the study (participation rate 82.1%). Among the participants, 4269 (49%) were men and 4471 (51%) were women, while 31% were residents in urban, 34% in suburban and 35% in rural areas; the age range was 19–99 yrs, mean 47 yrs (S.D. 17.7). As reported previously [14], using Pearson correlation coefficients, we found significant similarities in terms of age and sex distribution between the study participants, the total target adult population and the total adult population of Greece, even when the data were analysed separately for urban, suburban and rural populations. Logistic regression showed no effect of non-selection and random selection of suburban and rural populations on the study results. Moreover, no significant difference was found between non-responders and responders in terms of age, sex and prevalence of rheumatic symptoms or disease. The reasons

TABLE 1. Demographic and clinical variables of the RA patients

Variable	Total ($n=59$)	Males ($n=13$)	Females ($n=46$)	P
Age (yrs), mean (S.D.)	54.6 (15.1)	52.6 (16.3)	55.1 (14.9)	NS
Disease duration (yrs), mean (S.D.)	12.1 (11.2)	11.2 (8.0)	12.3 (12.0)	NS
Age at disease onset (yrs), mean (S.D.)	42.4 (11.7)	41.5 (12.5)	42.7 (11.5)	NS
Rheumatoid factor present	68 (56.1–79.9)	62 (31.6–86.1)	70 (56.8–83.2)	NS
Remission	29 (17.4–40.6)	31 (9.1–61.4)	28 (15–41)	NS
ACR functional classes II—IV	49 (36.2–61.8)	31 (9.1–61.4)	54 (39.0–69.1)	NS

Values are percentages (95% CIs) unless otherwise stated; NS = not significant.

for non-participation were unrelated to the presence or not of rheumatic disease.

Prevalence of RA

Of the 8740 participants, 59 were diagnosed as having had RA (Table 1). Thus, the age- and sex-adjusted prevalence of RA in the total target adult population was 0.67% (95% CI 0.54–0.80), while the prevalence of RA among the study participants was 0.68% (95% CI 0.51–0.85). The prevalence of RA was significantly higher among females (1.0%, 95% CI 0.71–1.29) compared with males (0.3%, 95% CI 0.14–0.46) in the study participants ($P < 0.0005$), with a ratio of 3.3:1. The prevalence of RA increased significantly with age up to and including the 50–59-yr-old group ($P < 0.002$), and then decreased slightly but non-significantly in the last two age groups ($P = 0.44$) (Fig. 2). There was no significant difference in the prevalence of RA among the urban, suburban and rural populations, nor between the selected and non-selected populations, nor even between the studied northern, central and southern areas of the country.

Logistic regression analysis showed that among the many factors included in the model, only female sex and age $\geq$40 yrs were significantly associated with RA [adjusted odds ratios 3.7 (95% CI 2.0–6.9), $P < 0.0005$, and 6.1 (95% CI 2.8–13.4), $P < 0.0005$, respectively].

Management of RA

Two of the 59 RA patients (3%, 95% CI 0.4–11.7) had not been seen by a physician prior to the study and were diagnosed by the investigators. Although the other 57 RA patients had sought medical assistance for their symptoms, on their first medical visit only 11 patients (19%, 95% CI 9.7–30.9) had consulted a rheumatologist and the remaining 46 (78%, 95% CI 67.4–88.6) had seen physicians of other specialties (Table 2). However, most of the RA patients were seen by rheumatologists at subsequent medical visits, and remained under their care: 36 of the RA patients (61%, 95% CI 48.6–73.4) had consulted a rheumatologist during the first year of the course of the disease (group I) and 18 (30%, 95% CI 18.3–41.7) after the first year of the course of the disease (group II), while five patients (9%, 95% CI 2.8–18.7) had never seen a rheumatologist. Table 3 shows the demographic and clinical variables for the RA patients in groups I and II. Multiple logistic regression analysis showed a significant negative association of an early consultation with a rheumatologist and of DMARD combination therapy with ACR functional classes II–IV [adjusted odds ratios 0.18 (95% CI 0.04–0.85), $P < 0.031$, and 0.17 (95% CI 0.04–0.72), $P < 0.016$, respectively].

Prior to being seen by a rheumatologist, 25 RA patients had been treated at different times by at least two non-rheumatologist physicians. Comparative data on the diagnosis and treatment of the RA patients by rheumatologists, orthopaedists and internists are shown in Table 4. The five most commonly prescribed DMARDs in 52 patients were: methotrexate (81%), hydroxychloroquine (46%), gold salts (37%), sulfasalazine (23%) and ciclosporin (21%). DMARD combination therapy was

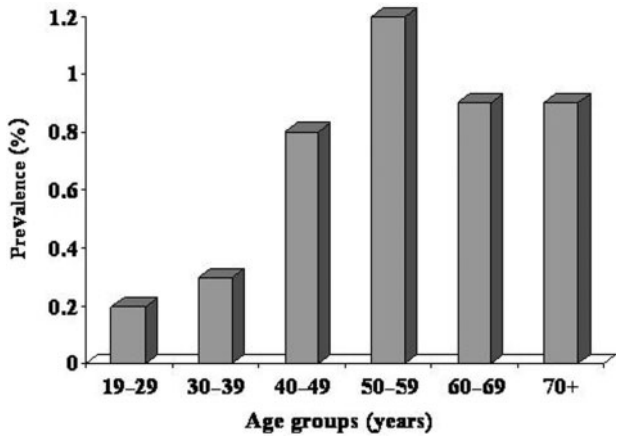

FIG. 2. Prevalence of RA by age group.

TABLE 2. Medical specialties first visited by the 59 RA patients

Medical specialties	No. of RA patients
Rheumatologists	11 (19%, 95% CI 9.7–30.9)
Internists	21 (36%, 95% CI 23.6–49.1)
Orthopaedists	19 (32%, 95% CI 20.6–45.6)
Other	6 (10%, 95% CI 3.8–20.8)
None	2 (3%, 95% CI 0.4–11.7)

administered in 21 patients and the most commonly used combinations were hydroxychloroquine + sulfasalazine + methotrexate in six patients (29%), hydroxychloroquine + methotrexate in five patients (24%), and methotrexate + ciclosporin in four patients (19%). Leflunomide and biological therapy were not available in Greece at the time the study was conducted.

Discussion

In this part of the ESORDIG study, the prevalence and management of RA were assessed in urban, suburban and rural general adult populations of Greece. Among the study participants the RA prevalence was 0.68%; this was significantly higher among women than men, and increased significantly with age up to and including the 50–59-yr-old group, and then decreased slightly. An early consultation with a rheumatologist and a DMARD combination therapy were negatively associated with ACR functional classes II–IV.

Our estimate of RA prevalence is comparable with that found in other population-based studies in European Caucasians, which used the same classification criteria [15]: 0.8% in Finland [3] and Manchester and Norfolk, UK [2, 19], 0.62% in Brittany, France [4], and ~0.5% in Sweden [5], Oslo, Norway [6], and Spain [7]. In a few studies from southern Europe [8–10], including Greece,

TABLE 3. Demographic and clinical variables of the RA patients by early or late consultation with a rheumatologist*

Variable	Group I ($n=36$)	Group II ($n=18$)	P
Females	81	72	NS
Age (yrs), mean (S.D.)	55.6 (14.7)	53.7 (13.1)	NS
Disease duration (yrs), mean (S.D.)	12.2 (12.3)	13.0 (9.5)	NS
Age at disease onset (yrs), mean (S.D.)	43.3 (11.9)	40.8 (9.5)	NS
Rheumatoid factor present	69 (51.9–83.7)	78 (52.4–93.6)	NS
DMARD combination therapy	36 (20.8–53.8)	44 (21.5–69.2)	NS
Remission	36 (20.8–53.8)	22 (6.4–47.6)	NS
ACR functional classes II–IV	42 (25.5–59.2)	72 (46.5–90.3)	0.034

Values are percentages (95% CIs) unless otherwise stated; NS = not significant.
*Group I: patients consulted a rheumatologist during the first year of the disease course; Group II: patients consulted a rheumatologist after the first year of the disease course.

TABLE 4. Diagnosis and treatment of the RA patients by rheumatologists and non-rheumatologists*

	Patients treated by		
	Rheumatologists ($n=54$) % (95% CI)	Orthopaedists ($n=34$) % (95% CI)	Internists ($n=30$) % (95% CI)
Correct diagnosis	100 (93.4–100.0)	18 (6.8–34.5)	17 (5.6–34.7)
Treatment			
NSAIDs	91 (79.7–96.9)	94 (80.3–99.3)	87 (69.3–96.2)
DMARD monotherapy	55 (41.7–68.3)	0 (0.0–10.3)	3 (0.1–17.2)
DMARD combination therapy	39 (26.0–52.0)	0 (0.0–10.3)	0 (0.0–11.6)
Corticosteroids	39 (26.0–52.0)	18 (6.8–34.5)	17 (5.6–34.7)
Physical therapy	44 (30.8–57.2)	27 (12.9–44.4)	20 (7.7–38.6)
Other**	43 (29.8–56.2)	44 (27.2–62.1)	33 (17.3–52.8)

NSAIDs: non-steroidal anti-inflammatory drugs; DMARD: disease-modifying antirheumatic drug.
*Prior to their visit to a rheumatologist, 32 patients had been treated by orthopaedists and 30 by internists. In addition, two patients had been continuously followed up by orthopaedists.
**Analgesics, local or intra-articular injections of corticosteroids.

and in a recent report from France [20], a lower prevalence of RA (0.18–0.34%) has been reported. Although this low prevalence could be related to a variation in genetic and/or environmental risk factors in these areas, it seems more possible, however, that different methodological approaches are responsible. For instance, the study in the Ioannina district of northwest Greece was based on RA cases diagnosed in two hospitals and private rheumatologists' offices [8]. Thus, an underestimation of the RA prevalence seems quite possible, since patients with severe RA could have moved and sought healthcare in other cities outside northwest Greece, while mild cases in the community could have remained undiagnosed or they could have been under the care of other medical specialties [21]. Indeed, it was shown in the present study that 9% of the RA patients had never been seen by a rheumatologist, while during the first year of their disease course only 61% of the patients had consulted rheumatologists. An underestimation is also possible in the Belgrade study [9]; 18% of the subjects with rheumatic complaints refused to undergo clinical evaluation, while patients with RA in remission were apparently not included in the prevalence estimation, since the questionnaire used focused on symptoms during the 3 months prior. The low response rate in the Italian study may be related to an underestimation of the RA prevalence [10], since patients with RA could have been unwilling to participate in a mail survey. On the other hand, genetic and/or environmental factors could account for the higher prevalence (~1.0%) in the USA [22, 23], the high prevalence of RA in Native American populations (up to 6.8%) [1], the low prevalence in Asian countries (~0.3%) [1, 24], the rarity of RA in Africans [1], and the lack of RA in Native Australian populations [25].

Female sex and age ≥40 yrs were strong independent predictors for the disease, in our study. With the exception of a Swedish study [5], the preponderance of RA in females is well documented in European, North American, Asian and Australian epidemiological population studies, with a female to male ratio varying in the range of 2–5.6:1 [1, 4, 6–10, 20, 22, 23]. In accordance with previous studies [1, 4, 7, 8, 22], RA prevalence increased with age reaching a peak in the 50–59-yr age-group. The slight decline of RA prevalence at older ages, we found, has also been reported in previous studies [4, 7, 8]; this could be attributed to an increased mortality rate in RA patients at these ages [26, 27]. The residential area did not affect the prevalence of RA in our study. However, some studies have suggested that rural residence may be associated with a lower prevalence [7, 28]. Whether a variation in environmental or socioeconomic factors could be responsible for these differences is unknown, although no association between socioeconomic status and RA was found in our study.

Prior to the present study, most of the RA patients had been treated by a rheumatologist. However, on their first medical visit, only a small percentage of RA patients (19%) had consulted rheumatologists, while within the first year after disease onset, 61% had visited rheumatologists; the latter finding is comparable with that of a recent study from Germany [12]. This delay in consulting a rheumatologist may be related to the low percentage (18%) of correct RA diagnosis made by non-rheumatologist physicians in our study and possibly to a low level of public awareness of RA. Delayed rheumatological care may have tremendous consequences on the outcome of the disease. Indeed, logistic regression showed a significant negative association between early rheumatological care and ACR functional classes II–IV. DMARD combination therapy was exclusively prescribed by rheumatologists and it is of interest that a significant negative association was also found between this therapy and ACR functional classes II–IV. Therefore, the early and aggressive treatment prescribed by rheumatologists may account for the above findings. The advantages of rheumatological *vs*

non-rheumatological care with regard to the outcome of the disease have already been stressed [29]. Concerning the correct diagnosis and treatment of RA, the results of the non-rheumatologist physicians were disappointing in our material, as compared with rheumatologists; we have recently published similar findings concerning patients with seronegative spondyloarthropathies [30]. The rheumatologists had correctly diagnosed and properly treated all the RA patients. About 88% of the patients had taken DMARDs and this is a slightly higher percentage than that reported in studies from Spain (72%) [11], France (82.1%) [31] and Canada (84%) [13]. In the present study, methotrexate was by far the most commonly employed DMARD for RA, as in other European studies [31, 32].

There may be a risk of selection bias in population-based studies. Since the participation rate in our study was high (82.1%), selection bias is only a remote possibility. Furthermore, analysis of the data of a random sample of non-responders indicated no significant difference from responders with respect to age, sex and prevalence of rheumatic symptoms or disease. Logistic regression showed that the random selection and non-selection of suburban and rural populations had no effect on the prevalence of RA.

The data on the prevalence and management of RA at the level of the general adult population presented in this article were derived directly from one-to-one interviews and clinical and laboratory evaluation of the study participants by rheumatologists. The studied regions were located in northern, central and southern mainland Greece and their adult population was representative of the total Greek adult population in terms of age and sex distribution. Therefore, the results of this study could reasonably be considered as representative of the general adult population of Greece, in terms of RA prevalence and management.

In conclusion, our findings indicate that the prevalence of RA in the adult general population of Greece is quite similar to that in many other European countries. Early consultation with a rheumatologist and DMARD combination therapy are associated with a better RA outcome in terms of global functional status.

Rheumatology	Key messages
	• Rheumatoid arthritis prevalence in the general adult population of Greece is similar to that in many other European countries. • Rheumatoid arthritis prevalence is higher among women than men and increases with age. • Early consultation with a rheumatologist and DMARD combination therapy are associated with a better RA outcome.

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The authors have declared no conflicts of interest.

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Clinical Vignette

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Wegener's granulomatosis presenting as a disappearing renal mass

A 40-yr-old man presented with fever, flank pain, epistaxis, haemoglobin 12.8 g/dl, WCC $12.9 \times 10^3/mm^3$, C-reactive protein (CRP) 142 mg/l and erythrocyte sedimentation rate (ESR) 101 mm. Computed tomography (CT) of abdomen showed a left renal mass, suggesting renal cell carcinoma (RCC) (Fig. 1A) and possible metastases (Fig. 1B) on CT thorax. Following discussions, it was agreed that the radiological features were atypical for RCC, and renal abscess was more likely. Patient remained unwell after 6 weeks of antibiotics. CRP was 320 mg/l and ESR 124 mm. No organisms grew on blood/urine culture. cytoplasmic-Anti-neutrophil cytoplasmic antibody was 1:320 with strongly positive anti-PR3, suggesting Wegener's granulomatosis (WG). Biopsy of the renal mass was planned.

Pre-biopsy CT abdomen confirmed considerable reduction in the size of the mass and new lesions in both the kidneys (Fig. 2A) compatible with vasculitis. Repeat CT thorax showed new peribronchial shadowing (Fig. 2B). Renal function deteriorated acutely and decision was made to treat for WG. Dramatic improvement was noted. He remains well. Full blood count, renal function and CRP are normal.

Maguire *et al*. [1] reported atypical radiological findings in 31 WG patients; only one had a renal mass. Spontaneous resolution of the mass makes our case unique. We believe that the mass represented oedema surrounding the underlying vasculitis. Renal biopsy, while important, should not delay treatment if the overall picture is suggestive of WG.

The authors have declared no conflicts of interest.

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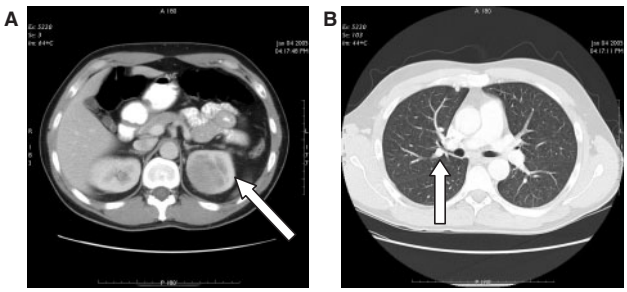

Fig. 1. Initial CT showing the renal mass and pulmonary nodule (marked with arrows).

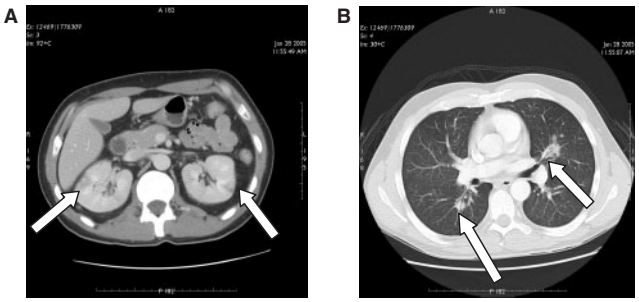

Fig. 2. Repeat CT with marked reduction in the renal mass and new renal and pulmonary lesions (marked with arrows).

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