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Monoclonal proteinaemia and solid tumours

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Abstract

A higher prevalence of solid tumours in patients with M(onoclonal) proteinaemia without a co-existing haematological malignancy has been reported. We investigated this association by linking a population-based registry of patients with newly diagnosed M-proteinaemia ($n = 1464$) with the Regional Cancer Registry. Patients were followed for a median of 7.4 years for those still alive. In total 167 (11%) patients with 173 solid tumours were compared with 861 patients with 'M-proteinaemia only' (without a haematological malignancy). The M-protein isotype or level or clinical parameters did not differ between the groups. M-protein isotype was not associated with a specific tumour type. Standardised Morbidity Ratios (SMR) for nearly all solid tumours were elevated in the year of the M-protein discovery, but the excess risk disappeared during follow-up suggesting selection through diagnostic investigations rather than a causal role. In this large series of patients with both newly diagnosed M-proteinaemia and a solid tumour no relationship could be established.

Keywords: M(onoclonal) protein; M(onoclonal) proteinaemia; Paraprotein; Solid tumour; Standardised morbidity ratio (SMR)

1. Introduction

For many decades, it has been assumed that in patients with monoclonal (M)-proteinaemia and without any evidence of a co-existing haematological malignancy, the prevalence of solid tumours is increased suggestive of a causal relationship [1–8]. Further analysis of this relationship could determine more exactly the incidence of this phenomenon in patients with a solid tumour and vice versa, thereby establishing the relevance of screening in cases of M-proteinaemia. To this end we linked a Dutch population-based M-protein database [9,10] to the regional cancer registry, and compared solid tumour M-protein patients with other groups in order to try to establish a time relationship between both diagnoses.

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2. Patients and methods

2.1. Patient population

From 1991 until 1993, a population-based registry on M-proteinaemia was set up in the region of the Comprehensive Cancer Center West (CCCW), a geographical area with 1.6 million inhabitants. Clinical chemists, internists, haematologists, pathologists and other physicians reported all patients with newly diagnosed M-proteinaemia or multiple myeloma in the CCCW area. Information on patients characteristics, laboratory test results, and results of bone marrow examinations and skeletal X-rays were documented. The M-protein-related diagnosis, co-morbidity and therapy were recorded. Follow-up was done annually. At follow-up, clinical data, any evolution into a haematological malignancy, appearance of any solid tumour, M-protein levels and other relevant laboratory tests were collected from the patients' hospital charts or from the general

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physician. In total, 1464 patients have been registered. The setup and contents of this registry have been described previously in [9,10].

2.2. Diagnostic criteria for monoclonal proteinaemia and solid tumours

M-proteins were detected either by agarose or by cellulose acetate electrophoresis, depending on the method used in the various hospitals involved. For inclusion in the registry, each M-protein had to be confirmed by immunotyping (immunofixation). The presence of a solid tumour preferably had to be confirmed by histology, otherwise a clinical diagnosis had to be based on at least radiological evidence of a tumour. Cancer sites were grouped according to the World Health Organization's International Classification of Diseases for Oncology (ICD-O) [11].

2.3. Linkage to the regional cancer registry

For verification and to ensure the completeness of our data on solid tumours, the database was linked to the regional database of the Netherlands Regional Cancer Registry [12]. In this cancer registry, all patients with newly diagnosed malignancies living in the CCCW region reported by the pathology laboratories are entered. The date of the cytological or histological confirmation constitutes the date of diagnosis. In addition, all hospitals employ a separate registry of the discharge diagnoses. For the present study, patient data were linked if the name, gender and date of birth were identical in both databases to exclude the probability of false-positive or false-negative linkages.

2.4. Solid tumour prevalence and incidence analysis

Follow-up started at registration (between 1991 and 1993) and is still ongoing. For the solid cancer linkage study, complete coverage with the Regional Cancer Registry was guaranteed until January 1st 1998. Endpoints were the development of a (haematological) malignancy or death, and patients still alive were censored for all other events on January 1st 2002. First, the prevalence of a solid tumour at first diagnosis was calculated. Patients were diagnosed with a M-protein-related solid tumour if the tumour was diagnosed within the timeframe of two years, one year preceding or following the discovery of the M-protein. Thus, all malignancies that could be associated with the M-protein, but were not present anymore due to treatment were included, as well as any asymptomatic multiple myeloma (MM), other haematological malignancies or solid tumours that developed later on. In cases of a simultaneous haematological malignancy or solid tumour during this period, the M-protein was considered to be associated with the former and not with the solid tumour.

Secondly, Standardised Morbidity Ratios (SMR) for the most prevalent tumours were determined for the period between registration (1991–1993) until January 1, 1998. Patients with newly diagnosed M-proteinaemia were at risk until the diagnosis of a solid tumour, multiple myeloma, other haematological malignancy was made or until they died. Multiplication of person-years under observation by the age-, gender-, and period-specific incidence rates yielded the number of solid tumours expected in the M-protein cohort if they experienced the same risk as was prevalent in the region of the CCCW. With this method, standardised incidence rates between patient and reference group were compared (indirect standardisation) and expressed as the ratio of the incidence rates (SMR), which may be viewed as a relative risk. Confidence limits for the SMR were based on a Poisson distribution for the observed number of deaths [13].

2.5. Statistical methods

Statistical methods to compare the 'M-proteinaemia Only' versus 'Solid tumour group' included Mann-Whitney's test and in the case of a case-control design, the chi-square test when appropriate. Analyses were performed using Statistical Package for the Social Sciences (SPSS) version 10. Data were entered in the database using SPSS Data Entry version 2 (both SPSS Inc. Chicago, IL, USA).

3. Results

3.1. Prevalence of solid tumours at first diagnosis of M-proteinaemia

The database consisted of 1464 patients with an initial diagnosis of M-proteinaemia. The frequency of newly discovered cases was 31/100,000 inhabitants and 189/100,000 for people above 70 years of age [9]. In 271 patients, a diagnosis of multiple myeloma was made, in 164 another haematological malignancy was diagnosed, but in the large majority no explanation was found (provisional [9] or definite monoclonal gammopathy of unknown significance, MGUS), (Table 1).

In total, 173 solid tumours without any evidence of multiple myeloma or other haematological malignancy were diagnosed in 167 (11%) patients. The types of tumour found are depicted in Fig. 1. Nearly all tumours ($n = 167$; 97%) were (adeno)carcinomas, the other six malignancies consisted of melanomas ($n = 4$), leiomyosarcoma ($n = 1$) and sarcoma ($n = 1$).

Table 1
Clinical characteristics in all diagnostic groups with M-proteinaemia

	Monoclonal proteinaemia only/MGUS	Solid tumour	*P*-value	Multiple myeloma[a]	Other haematological malignancies [b]
Number (%)	861 (59)	167 (11)		271 (19)	165 (11)
Gender M (%)	423 (49)	103 (62)	0.004	138 (51)	96 (58)
F (%)	438 (51)	64 (38)		133 (49)	69 (42)
Median age (range, years)	73 (17–103)	75 (37–95)	0.05	71 (28–93)	72 (21–94)
M	72 (20–103)	75 (37–95)	0.03	69 (28–89)	70 (20–89)
F	75 (17–98)	76 (47–92)	0.91	72 (40–93)	73 (25–94)
M-protein type and level (g/l)					
IgG (%)	618 (72)	29 (76)	0.45	155 (57)	75 (46)
Median (range)	10 (1–30)	10.5 (<1–85)		32.5 (6–117)	12.3 (<1–34)
IgA (%)	80 (9)	10 (6)	0.71	75 (28)	5 (3)
Median (range)	8.4 (4–31)	10 (2–47)		28.1 (5–81)	15.6 (2–25)
IgM (%)	159 (19)	30 (18)	0.19	4 (2)	81 (49)
Median (range)	7 (1–21)	10 (<1–30)		22 (2–57)	13.8 (2–110)

In the patient with prostate carcinoma, two haematological malignancies were observed: chronic lymphocytic leukaemia (CLL) and Hodgkin's lymphoma.

M, male; F, female; MGUS, monoclonal gammopathy of unknown significance.

[a] In five patients, a solid tumour was present (carcinoma of lung, breast, thyroid, ovary and unknown primary site).

[b] In eight patients, a solid tumour was present (melanoma, carcinoma of unknown primary site, bladder, prostate, colon, larynx, skin and liver).

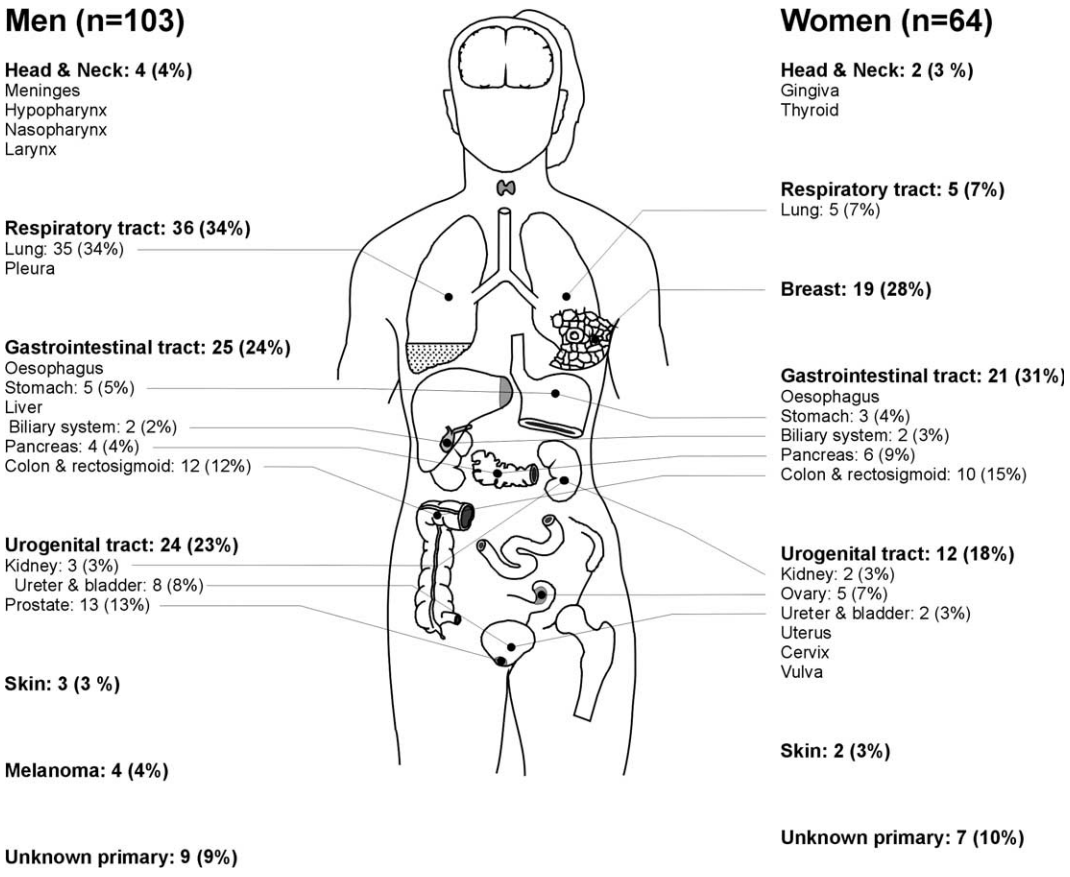

Fig. 1. Distribution of solid tumours and M-proteinaemia. Two tumours were diagnosed in six patients: bilateral breast (2), breast + pancreas, breast + colon leiomyosarcoma, squamous skin + melanoma, pancreas + gingiva. No percentage between brackets means only one tumour found. Modified from [19].

3.2. Solid tumour and M-protein isotype

To study whether specific tumour types were related to specific M-protein isotypes, we selected patients with one the six most frequently occurring solid tumours, lung ($n = 40$), colon ($n = 21$), breast ($n = 15$), prostate ($n = 13$), ureter and bladder ($n = 10$) and pancreas ($n = 9$). In all, the IgG isotype predominated (60–85%), followed by IgM (7–30%) and IgA (0–10%). No clear preferential M-protein types were seen within the specific tumour groups.

3.3. 'Solid tumour group' versus 'M-proteinaemia only group/MGUS'

To study whether patients with M-proteinaemia and a solid tumour (i.e. "Solid tumour Group") had specific characteristics in demographics or M-protein isotype and levels, we compared this group with the patients without any malignancy (Table 1). In the tumour group, male gender predominated. In addition, small, but significant, differences in age were seen. The distribution of M-protein isotypes and levels was identical with most patients expressing a median of approximately 10 g/l IgG monoclonal proteinaemia.

3.4. Response of the M-protein on cancer treatment

When M-proteins are causally related to a solid tumour, one would expect to find an increase of the M-protein levels during tumour progression and a decrease after tumour disappearance. In the Solid tumour group, 64 out of 167 patients died within one year after the detection of the M-protein leaving 103 patients with follow-up data. In 25 patients (median follow-up 37 months, range 3–95 months) the M-protein was measured at least once after the first detection and therapy (if any) for the solid tumour. Since in four patients a haematological malignancy developed (see Section 3.5), a relationship (rising or lowering of the M-protein in correspondence with the progression or decrease of the tumour) could be studied only in 21 patients. In this small group of patients, no convincing relationship was seen between the behaviour of the solid tumour and M-protein levels (data not shown).

3.5. Follow-up since entry in the M-protein database

During follow up (last analysis 1-1-2002) a new solid tumour was detected in 23 patients in addition to those already diagnosed in the 167 patients. All of these tumours occurred in the period 1992–1998 (see Table 2). In the years thereafter, no additional solid tumours were found. Out of the 167 patients in whom a solid tumour was diagnosed simultaneously with the M-protein, three patients developed multiple myeloma (14, 56 and 65 months after the detection of the M-protein) and one patient developed a non-Hodgkin's lymphoma (NHL) (28 months after the detection of the M-protein).

For comparison, in the Monoclonal proteinaemia only/MGUS group, 28 developed multiple myeloma, and another 17 developed a haematological malignancies, consisting of a NHL ($n = 12$), myelodysplastic syndrome or acute myeloid leukaemia ($n = 3$) or myeloproliferative disease ($n = 2$).

Table 2
Standardised morbidity ratios (SMR) for the most prevalent solid tumours in the year of discovery of the M-protein and the years after

Solid tumour (all (adeno) carcinomas)	Year of M-protein discovery (1991–1993)				Follow-up (1992–1998)			
	Observed number	Expected number	SMR	95% Confidence interval	Observed number	Expected number	SMR	95% Confidence interval
Men								
Lung	19	0.9	21.1	12.5–31.9	5	4.1	1.2	0.4–2.6
Colon and rectosigmoid	4	0.4	10	2.5–22.5	1	1.7	0.6	0–2.4
Prostate	5	0.9	5.6	1.7–11.6	3	4.5	0.7	0.2–1.7
Unknown primary	5	0.2	25	7.6–52.4	2	0.8	2.5	0.2–7.3
Pancreas	1	0.1	10	0–40	0	0.25	0	0–4
Stomach	2	0.3	6.7	0.6–19.4	0	0.8	0	0–1.3
Bladder	3	0.2	15	2.7–37.3	1	1.0	1	0–4.0
Women								
Lung	3	0.1	30	5.4–74.6	0	0.6	0	0–1.7
Colon and rectosigmoid	4	0.4	10	2.5–22.5	5	1.6	3.1	1.0–6.5
Breast	3	0.6	5	0.9–12.4	3	2.9	1.0	0.2–2.6
Unknown primary	5	0.1	50	15.2–104.7	2	0.6	3.3	0.3–9.7
Pancreas	4	0.1	40	10–90	2	0.4	5.0	0.4–14.6
Stomach	2	0.1	20	1.7–58.3	0	0.7	0	0–1.4
Bladder	0	0.1	0	0–40	1	0.29	3.5	0–13.8

3.6. Standardised morbidity ratio

Cumulative follow-up of all 1464 patients during this selected period (1991–1998) was 3060 person-years with a median follow-up of 1.3 years (range 0–7 years) for all patients, and a median follow-up of 7.4 years (range 10 months to 11 years) for those still alive. Cumulative follow-up (measuring the time interval between the date of diagnosis of the M-proteinaemia and the date of diagnosis of the solid tumour) for the Solid tumour group was 24 person-years (median less than 1 day, range 0–2.8 years). In conclusion, most solid tumours were diagnosed simultaneously with the detection of the M-protein (median interval between both diagnoses less than one day, see above). In the first year after the detection of the M-protein, SMR for nearly all solid tumours showed an increased risk (range 0–50). However, all declined sharply or normalised during the subsequent follow-up years (Table 2).

4. Discussion

In this population-based registry on patients with newly diagnosed M-proteinaemia, we describe the largest series collected thus far of patients with both a solid tumour and a M-protein, but without any evidence of a co-existing haematological malignancy. Since 1928, investigators have reported an increased prevalence of solid tumours in patients with M-proteinaemia suggesting a paraneoplastic phenomenon. For comparison with our cohort, we selected only studies with more than 100 patients, with a description of the related malignancy including concise histopathology and information on the determination of the M-protein, and were left with 8 [1–8]. Identical to our series, nearly all solid tumours described were (adeno)carcinomas. M-proteins were mostly of the IgG isotype and levels (if investigated) were generally lower than 30 g/l.

The co-existing tumours in this M-protein database were manifest at the diagnosis of the M-protein in the large majority of patients. During follow-up, only a small additional number of solid tumours were detected. Kyle and colleagues observed the development of a second tumour in 15 of 241 MGUS-patients during a 20–35 year follow-up [14] and Pasqualetti and colleagues reported 31 out of 263 similar patients who died due to a solid tumour during a median follow-up of 11.5 years [15]. In contrast, in the only prospective study investigating the incidence of hematological and solid malignancies in patients with M-proteinaemia, Gregersen and colleagues did not observe an increased risk of solid tumours in 1229 patients during follow-up (mean 4.8 years, range 0–15.7 years) [16]. Similar to our findings, the risk of developing a solid tumour was increased in the first year of follow-up, although this risk diminished thereafter [16].

Approaching the probable relationship between M-proteinaemia and cancer the other way around yielded no association either: in two cross-sectional studies, the prevalence of M-proteinaemia in patients with non-haematological tumours was not increased when compared with the prevalence in the general population [17,18].

In conclusion, we did not observe differences in clinical characteristics between patients with 'M-proteinaemia only/MGUS' and patients with 'Solid tumour and M-proteinaemia'. There was no relationship between specific solid tumours and M-protein isotype nor did the serum level of the M-protein change after the anti-tumour therapy (although the number of patients was small in this analysis). Although risks for nearly all solid tumours found were initially elevated in patients with newly diagnosed M-proteinaemia, these decreased in the year after suggesting a diagnostic selection of patients rather than a causal role.

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