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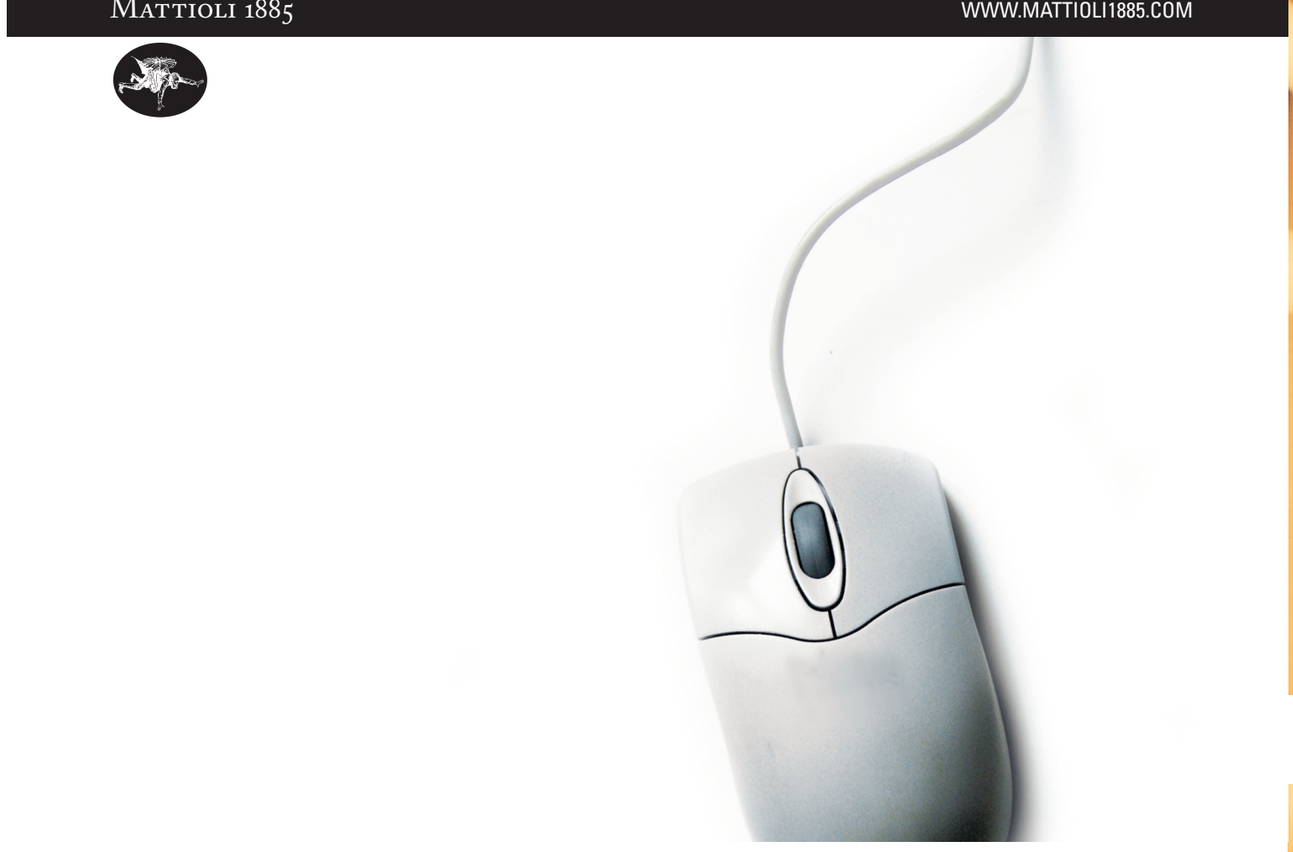

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Do modern methods of post-mastectomy immediate breast reconstruction for breast cancer delay adjuvant therapy?

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Summary. *Background and aim of the work:* Modern techniques of immediate breast reconstruction after mastectomies for breast cancer gives excellent cosmetic results and improve quality of life. However, it is perceived that immediate breast reconstruction may prolong recovery and can result in complications delaying adjuvant therapy. We aim to determine if there is such delay in the United Kingdom beyond the 31 days recommended by the National Institute for Health and Care Excellence. *Methods:* All patients who underwent mastectomy for breast cancer from January 2009 to August 2014 and received adjuvant treatment were categorised into three groups – mastectomy, implant / expander and flap. The primary end point was the time interval from the definitive surgical procedure to the start of adjuvant therapy. *Results:* Of the 192 patients (64 per group) analysed, mastectomy patients were significantly older, smokers and with higher nodal status ($p<0.05$). The groups were comparable with respect to other clinicopathological factors ($p>0.05$). Six patients from implant group and one patient from flap group started their adjuvant therapy within 31 days. The mean duration of adjuvant therapy was 63.2 days (33-202) in mastectomy group, 52.82 days (26-136) in implant group and 50.61days (29-89 days) after flap procedures ($p=0.004$). *Conclusions:* Our study shows a delay in initiating adjuvant therapy in keeping with published literature. The reasons could be multifactorial including delay in service provision. This delay is statistically significant in the mastectomy-alone patients, perhaps because they were older and smokers. Treatment pathways and multidisciplinary clinics will circumvent these concerns.

Key words: mastectomy, reconstruction, adjuvant therapy

1. Background and aim of the work

Breast cancer is one of the most common cancers in women worldwide, with 55122 new cases of invasive breast cancer being diagnosed in the United Kingdom in 2015 (1). The overall outcome in early stage breast cancer has improved considerably over the last two decades with a current overall 5-year survival of 87% in the United Kingdom. The reason for this improved outcome is multifactorial with advances in surgical techniques, adjuvant therapies, breast screening and public awareness as major contributing factors. With increase in life expectancy, the quality of life gains more importance. One vital aspect in improving the quality of life after mastectomy for breast cancer is reconstructing the breast.

Immediate breast reconstruction (IBR) after mastectomy for breast cancer has been shown to have a positive influence over the delayed reconstruction on body image and sexuality, improving psychosocial well-being, reducing anxiety levels, resulting in excellent patient satisfaction and improving self-esteem and quality of life (2-6). It may also avoid further admissions for planned surgical procedures (7).

A number of studies have shown that reconstruction is oncologically safe after mastectomy even in advanced disease (8-10). Current UK oncoplastic breast reconstruction guidelines (11) recommend that onco-

plastic breast surgery is discussed in 100% of patients requiring a mastectomy. Skin sparing mastectomy (SSM) has been shown to be oncologically safe with low local recurrence rates (12) and combined with immediate breast reconstruction provide superior aesthetic outcomes with less disruption to the patient's lifestyle (13). The United Kingdom national mastectomy and breast reconstruction audit 2011 (14) has shown that 3389 (21%) patients underwent immediate breast reconstruction out of the 16485 patients who had mastectomies during their study period of 15 months.

Modern techniques of IBR like Deep Inferior Epigastric Perforator (DIEP) flaps and Acellular Dermal Matrix (ADM) based implant reconstruction give excellent cosmetic results. There is a perception that these complex procedures may have prolonged recovery and can result in significant complications, which may unduly delay the initiation of adjuvant therapy or lead to its omission altogether. This is because adjuvant therapy after breast cancer surgery has shown to produce a significant survival advantage and reduction in local recurrence in selected patients (15, 16).

In a meta-analysis, 6 months of anthracycline-based poly-chemotherapy reduced the annual breast cancer death rate by about 38% for women younger than 50 years of age and by about 20% for those of age 50-69 years irrespective of the use of tamoxifen and of oestrogen receptor (ER) status, nodal status, or other tumour characteristics (15). In another large meta-analysis done by the Early Breast Cancer Trialists' Collaborative Group (16), for 1314 women with axillary dissection and one to three positive nodes, radiotherapy reduced locoregional recurrence ($p<0.00001$), overall recurrence (RR 0.68, 95% CI 0.57-0.82, $p=0.00006$), and breast cancer mortality (RR 0.80, 95% CI 0.67-0.95, $p=0.01$).

The optimum duration to start of adjuvant therapy after breast cancer surgery is not clearly defined. The National Institute for Health and Care Excellence, UK (NICE) has recommended that adjuvant therapy should be started by 31 days of completion of definitive surgery (17). American Society of Clinical Oncology (ASCO)/National Comprehensive Cancer Network (NCCN) quality measures recommends adjuvant chemotherapy within 120 days of diagnosis for women aged less than 70 years with stage II or stage III hormone receptor-negative breast cancer (18). The 120-day threshold was selected as a "reasonable estimate of the time required to deliver the preceding components of therapy that would not jeopardize outcome" (18).

Available evidence looking at the delay between IBR and adjuvant therapy have given mixed results and used data before the widespread use of the above modern methods of reconstruction. Most studies evaluated patients on an intention to treat basis (who received chemotherapy) rather than those for whom chemotherapy was indicated. This can miss patients who did not receive adjuvant therapy because of complications of breast reconstruction. Further, most studies only compared mastectomy with IBR without dividing the IBR group into implant based and free flap groups which are associated with different complications and recovery times.

Overall there is no clear consensus on the optimum time to give adjuvant chemotherapy or radiotherapy after surgery and mixed evidence on the effect of early initiation of adjuvant therapy after breast cancer surgery.

The aim of the study is to determine if modern methods of post-mastectomy immediate breast reconstruction delays the start of adjuvant chemotherapy or radiotherapy in the United Kingdom based on NICE recommendations and if there is difference between mastectomy, implant procedures and flap-based procedures in the time to start adjuvant therapy.

2. Methods

A retrospective audit was conducted in four hospitals of the Essex cancer network for the period from January 2009 to August 2014. All patients who underwent mastectomy for breast cancer and received adjuvant chemotherapy or radiotherapy were grouped into mastectomy without reconstruction (M group); mastectomy with implant-based reconstruction including ADM (I group) and mastectomy with flap-based reconstruction with pedicled and/or free flaps (F group). Patients who received neoadjuvant chemotherapy and those whose adjuvant therapy was delayed for social reasons or patient preference were excluded.

The primary end point for the study was the time interval from the final definitive surgical procedure for breast cancer to the first day of either adjuvant chemotherapy or radiotherapy. From this we plan to assess for any difference between the three groups in patients who started adjuvant therapy before 31 days and after 31 days of breast surgery. We also assessed for a difference in the mean duration to the start of adjuvant therapy between three different groups.

Surgical site complications recorded included infection, seroma, haematoma, skin flap necrosis and implant specific complications. Return to surgery and systemic complications were separately recorded. Complications were classified as minor if they were grade 1, 2 or 3a on the Clavien- Dindo system (19) and as major if the complications were grade 3b to 5.

From the results of Hamahata et al (20) a standard deviation of 13 days for the delay to adjuvant chemotherapy between the two groups (IBR and non-IBR) is assumed. Thus to compare two group means a minimum important difference of half a standard deviation is 6.5 days, and the minimum sample size required for a two-sample, two-sided t-test at the 5% significance level to give a power of 80% is 64 patients in each group.

Consecutive female patients, undergoing a total mastectomy and recommended to have adjuvant chemotherapy or radiotherapy were identified from the multidisciplinary (MDT) database for a period from March 2014 to August 2014. When data was collected over this 6-month period, the 64 patients required in the mastectomy group were obtained. In order to obtain the sample size of 64 patients in the implant and free flap group, the database was sequentially reviewed over the previous years.

For data description, categorical variables are presented as counts and analysed using Fisher's Exact test, and continuous variables are shown as mean, median, standard deviation, inter-quartile range, and range. For the statistical inference, the means of the delay to adjuvant chemotherapy for the three groups are compared using analysis of variance using a permutation F-test. Analyses have been performed using the computer program R (21). Model fitted means have been obtained using function effect from R package effects (22, 23). The permutation test for one-way analysis of variance has been done using function aovp from R package lmPerm (24). Bootstrap estimates and confidence limits have been obtained using functions boot and boot.ci from R package boot (25, 26).

This investigation is a quasi-experimental design and so the main purpose of the statistical analysis is to estimate the "group effects", that is the difference between the procedure means.

3. Results

192 patients were included in the study (64 in each of the three groups). There is a statistically significant difference between the three groups with respect to age, smoking and previous breast surgery ($p<0.05$ for these variables). The groups were comparable with respect to BMI, ASA grade, previous radiotherapy and contralateral surgery as shown in Table 1.

There is a statistically significant difference between the three groups with respect to nodal status ($p=0.0007$). The groups were comparable with respect to type of breast cancer, tumour size, grade, ER, Her 2 status and LVI as shown in Table 2.

Six patients in the implant group and one patient in the flap group but no patient in the mastectomy group started adjuvant therapy within 31 days. Since only 7 patients out of 192 started their adjuvant therapy within 31 days, no clinically significant conclusions can be drawn from its analysis. The mean duration to the start of adjuvant therapy after surgery was 63.2 (33-202) days for the mastectomy group, 52.82 (26-136) days for the implant group and 50.61 (29-89) days for the flap group. Starting of adjuvant radiotherapy (when given without chemotherapy) was longer after surgery in all three groups compared to the duration to the starting of adjuvant chemotherapy. Fisher's Exact Test P-value for association between time to adjuvant therapy category and procedure is 0.019 using 10000 simulations indicating that the variation among the means for the three procedures is statistically significant.

The following graph shows the mean and 95% confidence limits for the procedure means based on the underlying statistical model implied by the analysis of variance, and in particular the single estimate of var-

Table 1. Patient characteristics

Characteristics	Factors	Mastectomy (n=64)	Implant (n=64)	Free Flap (n=64)	Fischer Exact Test using 10000 simulations
Age	Mean (Range)	59.34 (33-86)	50.2 (27-74)	50.61 (32-83)	ANOVA - significant
BMI	Mean (Range)	27.1 (17-33.8)	25.9 (18-37)	26.1 (19-34)	Permutation test p 0.476
Smoking	Yes	16	4	2	**p 0.0004**
	No	45	52	49	
	Unrecorded	3	8	13	
Previous Surgery	Yes	4	4	15	**p 0.0002**
	No	60	59	43	
	Unrecorded	0	1	6	
Previous Radiotherapy	Yes	3	3	4	p 0.070
	No	61	60	54	
	Unrecorded	0	1	6	
ASA Grade	1	28	31	25	p 0.059
	2	31	27	32	
	3	5	1	1	
	Unrecorded	0	5	6	
Contralateral Surgery	Yes	13	12	8	p 0.485
	No	51	52	56	

iance provided by the residual mean square. However, the means can be regarded as a diversion as the purpose of the study is not to estimate procedure means but to estimate the differences between the procedure means.

The following graph shows the differences between the procedure means. The nominal 95% confidence level has been adjusted by the Dunn-Sidak method (27) to allow for the multiplicity of comparisons which requires a 98.3% confidence level.

The confidence limits for (M-F) and (M-I) do not enclose zero and so these differences between the means would usually be regarded as statistically significant.

3.1 Complications and its impact on delivery of adjuvant therapy

Implant patients had the highest complication rate of 28.1% (6 - infection, 2 - bleeding and 3 - skin necrosis accounting for 17.2% major along with 10.9% minor) compared to flap patients who had a complication rate of 18.8% (4 infection, 4 - bleeding, 2 - skin necrosis and 1 - flap necrosis accounting for 17.2% major along with 1.6% minor) and mastectomy group (1 - infection and 1 - bleeding which is 3.1% major along with 9.4% minor). This was statistically significant. Infective complications were the commonest reason which resulted in a delay to the start of adjuvant therapy. The probability p=0.036 as shown in table 3 indicates that the variation among the means for complications is statistically significant. The residual variance is 556.79 and its bca bootstrap 95% confidence limits are (329.61, 1044.95).

The residual standard deviation is 23.60 and its bca bootstrap 95% confidence limits are (18.14, 32.31).

The grand mean is 55.55 and its bca bootstrap 95% confidence limits are (52.71, 59.66).

The coefficient of variation % is 42.5 and its bca bootstrap 95% confidence limits are (33.9, 54.6).

3.2 Service delays

Mastectomy/implant and free flap patient groups were respectively discussed in MDT in 16.69/18.13/12.7 days and attended oncology appointment in

Table 2. Tumour characteristics

Characteristics	Factors	Mastectomy (n=64)	Implant (n=64)	Free Flap (n=64)	Fischer Exact Test using 10000 simulations
Types	Ductal	45	53	56	p 0.080
	Lobular	14	6	7	
	Others	5	5	1	
Tumour stage	T0	0	0	2	p 0.054
	T1	9	10	11	
	T2	40	45	36	
	T3	9	10	11	
	T4	0	1	14	
	Unrecorded	6	3	0	
Nodal stage	N0	11	29	22	p 0.0007
	N1	32	28	35	
	N2	12	2	6	
	N3	1	0	0	
	Unrecorded	8	5	1	
Grade	1	2	3	1	p 0.054
	2	30	17	27	
	3	26	42	34	
	Unrecorded	6	2	2	
ER status	Positive	48	51	54	p 0.671
	Negative	13	12	9	
	Unrecorded	3	1	1	
Her 2 status	Positive	20	19	13	p 0.598
	Negative	41	42	49	
	Unrecorded	3	3	2	
LVI	Yes	33	27	17	p 0.053
	No	24	26	32	
	Unrecorded	7	11	15	

Table 3. Analysis of variance of Days to adjuvant therapy by Complications, using bootstrapped goodness of fit statistics, and using a permutation F test probability

Source of variation	Degrees of freedom	Sum of squares	Mean square	F ratio	Permutation F test probability	Partial eta squared
Complications	2	3906.7	1953.4	3.51	0.035	0.036
Residual	189	105232.8	556.8			
Total	191	109139.5				

16.13/9.08/10.1 days but received adjuvant treatment after another 29.18/25.61/27.81 days. This shows the initiation of treatment was significantly delayed on all groups irrespective of complications or oncology appointment due to service delays.

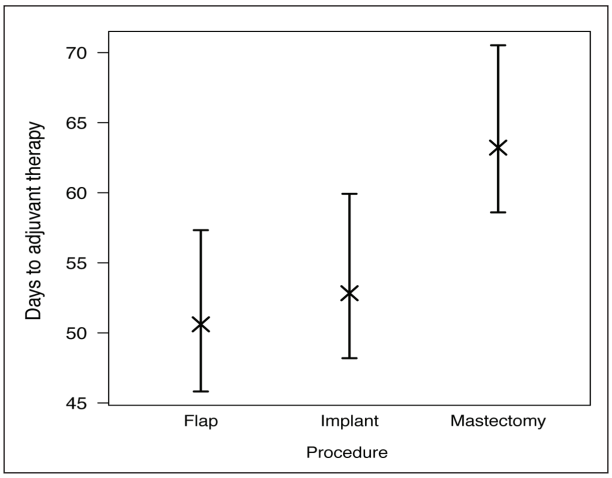

Figure 1. Means of Days to adjuvant therapy for Procedure and bootstrap 95% confidence limits

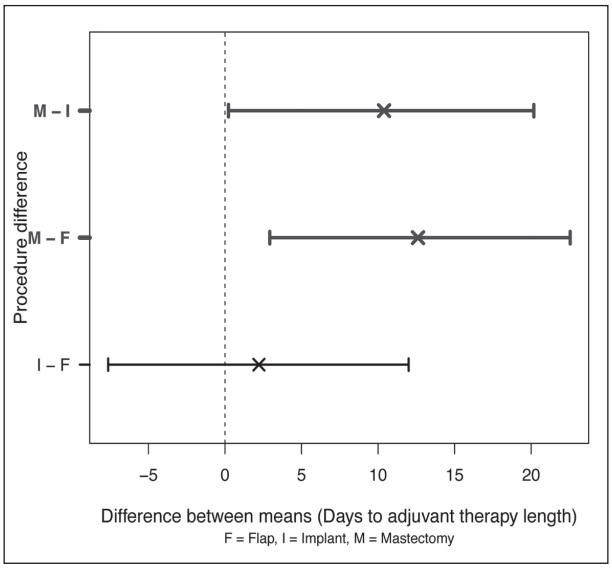

Figure 2. Differences between mean of Days to adjuvant therapy for Procedure and bootstrap 98.3% confidence limits

4. Discussion

It is well established that breast reconstruction after mastectomy improves the quality of life and in fact the improved psychological outlook is more pronounced in IBR compared with delayed reconstruction (28). While IBR has been suggested to be oncologically safe, there remains a concern that its complication rates may be higher than mastectomy without reconstruction (29-31) and this may unduly delay the initiation of systemic chemotherapy or lead to its omission altogether (7, 32, 33). This study looked at the effects of modern methods of breast reconstruction like DIEP flap and ADM based implant reconstruction on delivery of adjuvant chemotherapy and radiotherapy.

In this study, the patients in the mastectomy group were found to reflect the patient characteristics in the series by Zhong et al (34) in which patients having mastectomy alone were older (median age 51 vs. 45 years, $p<0.0001$) and more likely to be smokers (14% vs. 5%, $p=0.007$). This may represent a selection bias where younger fitter patients request and accept immediate reconstruction more readily.

The patients undergoing IBR were significantly more node negative and there were also more T3 and higher grade tumours in the flap group but were not statistically significant. In the review by Chang RJ et al (35), there were more women with stage I and II tumours in the IBR group compared to the group who received mastectomy alone (72.0% versus 57.5%, $p=0.034$) and also had fewer positive nodes and more grade I and II tumours (42.4% versus 63.6%, $p=0.006$).

Only 7 patients out of 192 (6 in the implant group and one patient in the flap group) met the NICE target of 31 days to the start of adjuvant therapy after final surgery. This is mainly a reflection of the service delays. Most published series show a time to start of adjuvant therapy of more than 31 days. In the 2012 NHS Breast Screening Program (NHSBSP)/Association of Breast Surgery (ABS) national audit of adjuvant therapy for screen-detected breast cancers diagnosed in 2009/10, in the whole of UK, the median time from final surgery to radiotherapy was 60 days (inter-quartile range 48-74 days) (36). Fewer than 50% of women received radiotherapy within eight weeks of their final surgery (37).

In our results, patients who had mastectomy without reconstruction had a greater delay to start adjuvant therapy compared to reconstructed patients. This is also highlighted in the series by Allweis (38) with 52.7 (range 1 to 215) days for mastectomy alone versus 40.6 (range 14 to 131) for patients with reconstruction. This observation may be explained by the finding that mastectomy patients were older, more likely to be smokers and less fit prolonging the recovery from surgery.

In this study, we found an overall complication rate of 12.5% for mastectomy patients, 28.1% for implant patients and 18.8% for flap patients. This reflects the trend shown in other series like Mortenson et al (39) where complications in patients who underwent immediate breast reconstruction compared with those who did not was 17/76 [22.3%] vs 6/72 [8.3%]; p=0.02. In the review by Zhong et al (34) patients undergoing mastectomy alone had a 3.7% major complication compared to 15.5% in the IBR group (p<0.0001). In the series by Shikhman et al (40), there was a 15.3% complication rate in 98 non-IBR patients compared to a 24.2% complication in 66 IBR patients. Those with complications had a statistically significant delay to initiation of chemotherapy (42.5 days vs 60.6 days, p=0.013). According to our results, the higher complication rate in our reconstruction group did not lead to an overall delay in starting adjuvant therapy. This may be because many of the complications after reconstruction like bleeding and skin or flap necrosis are dealt with by early further definitive surgical procedures without delaying recovery significantly.

Apart from the patient, tumour and surgical factors discussed above, service delivery capacity will also affect the time to delivery of adjuvant therapy. These include the time required for pathologic assessment of the tumour, referral wait time to see an oncologist and capacity to deliver chemotherapy or radiotherapy. This study was conducted in a single region of the United Kingdom which is likely to provide similar capacity to deliver adjuvant therapy thereby limiting this effect on our results. Alderman AK (41) found that in addition to age, other clinical and socio-demographic characteristics place patients at increased risk for delayed chemotherapy. Taylor et al (42) found that the reasons for late chemotherapy initiation in the non-reconstructed group included the need for pathology review and social reasons like patient holidays.

Treatment pathway management can minimise the total time from final surgery to the start of adjuvant therapy (37). Multi-disciplinary teams should plan adjuvant therapy well ahead to try to ensure that women have their treatment at the earliest appropriate time (37). Seeing patients in a combined breast clinic with surgeons, oncologists and breast care nurses as soon as possible after the postoperative MDT can reduce some of the service delays. There are considerable regional differences in service provision for radiotherapy in the UK. From the 2009/10 breast screening data, the median number of days varied from 53 days in North West, to 69 days in South East Coast (36). Our study was conducted as a multicenter audit which increases its applicability to other NHS trusts in the UK.

4.1 Limitations of this project

Our data has been collected as a retrospective study and has limitations compared to a prospective trial. There might be unaccounted factors that could be associated with patient characteristics, treatment choice and timing of delivery of adjuvant therapy resulting in bias. All free flap reconstructions were performed at one centre which has one of the highest volumes of free flap breast reconstruction in Europe and the results may not translate to small volume centers.

5. Conclusion

In conclusion, this study shows that the majority of patients undergoing mastectomy regardless of IBR will have a delay to the start of adjuvant therapy beyond 31 days. Patients who underwent mastectomy alone had a statistically significant delay to the start of adjuvant therapy compared to the implant and free flap groups, but this group of patients were older and more likely to be smokers. The clinical significance of this delay is not clear. The incidence of postoperative complications was significantly higher after IBR than mastectomy alone. Patients who had post-operative complications had a delayed start of adjuvant therapy compared to patients who made an uncomplicated recovery.

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The relationship between clinicopathology factors and omental metastasis in epithelial ovarian cancer

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Summary. *Background*: Aside from being a major metastatic site in epithelial type ovarian cancer, omentum has an immunological role. Omentum has the ability to colonize the spread of cancer cells by forming omental caking. This study aims to determine the relationship between clinicopathology factors with metastasis in omentum in epithelial type ovarian cancer. *Methods:* The study used cross-sectional study design. Subjects were patients diagnosed with epithelial type ovarian cancer who underwent surgery at Cipto Mangunkusumo Hospital between January 2010 and December 2017. *Results*: There were association between serous as well as mucinous type, omental nodules, and between CA 125 and metastasis in omentum (OR 1.7, CI 95% 24.1-47.7; p=0.002, OR 14.5, CI 95% 2.5-82.2; p=0.002, OR 61, CI 95% 11.4-324.8; p<0.01, and OR 3.5, CI 95% 1.2-9.7; p=0.013). Multivariate analysis demonstrated a significant association between mucinous types with metastases in the omentum (aOR 9.71, CI 95% 1.11-84.89; p=0.04) and between the omental nodules and metastases in the omentum (aOR 40.92, CI 95% 6.64-251.96 ; p <0.01). *Conclusions:* The incidence of omental metastasis in epithelial ovarian cancer is higher in mucinous histological types of and omental nodules only.

Key words: clinicopathology factors, epithelial ovarian cancer, omentum, omental metastasis

Introduction

According to the National Cancer Institute, the incidence of ovarian cancer in America in 2015 was 11.6 per 100,000 women (1). In Indonesia, Indonesian Society of Gynecology Oncology (INASGO) reported that new cases of epithelial type ovarian cancer from 2015, 2016 and 2017 were 463 cases, 379 cases and 280 cases, respectively (2). Particularly, in Cipto Mangunkusumo Hospital, Jakarta, Indonesia, there were 397 epithelial ovarian cases during the period of 2010 to 2017, with serous type cancer as the most common type (3).

Several factors are associated with the prognosis of omental metastasis and occult metastasis. The most histological type in which omental metastasis occurs is the serous type, and the most degree of differentiation which metastasis to the omentum is the third-degree (4-6). Almost all omental nodules are positive for microscopic metastasis. However, there are a few cases of hidden metastases in the omentum (5, 7). The size of the tumor is also related to the prognosis of ovarian cancer: those with early stages of ovarian cancer have a tumor size greater than in the late stages of ovarian cancer (8). Ascites is also a clinical prognostic factor that distinguishes between benign and malignant adnexal masses before surgery (9). The presence of ascites and CA 125 levels increases the incidence of hidden metastases in early-stage ovarian cancer (4, 6).

Omentum is a major site for intraperitoneal metastases in epithelial type ovarian cancer (7, 10, 11). Several studies have suggested that of patients with early-stage ovarian cancer, who are macroscopically confined to the ovary and then undergoing surgical staging, 29% -36% of them turned out to have an elevated stage due to metastasis in the omentum,

peritoneum, and retroperitoneal lymph nodes (4, 12). Omentectomy is one of the procedures for surgical staging according to FIGO (7, 13). Despite being a common site for metastasis, omentum also has a protective function; it has an immunological role in the presence of milky spot structures. Omentum contains macrophages, T cells and B cells in the omentum stroma (11, 14). In addition, milky spots and adipose tissue cause colonization of cancer metastases cell in the omentum in the form of omental caking, which can localize the metastatic process (15, 16). Due to the role of omentum, studies are required to determine the relationship between clinicopathological factors associated with metastasis in omentum in epithelial type ovarian cancer. Therefore, we could determine whether omentectomy is needed in cases of epithelial ovarian cancer.

Methods

We used a cross-sectional study design by evaluating medical records of patients diagnosed with epithelial type ovarian cancer who underwent surgery at Cipto Mangunkusumo Hospital, Jakarta, Indonesia during the period between January 2010 and December 2017. Those with epithelial ovarian cancer from anatomical pathology report and performed omentectomy based on the surgery report were included in the present study. Those who had received chemotherapy therapy or had previously been operated at an outside hospital were excluded. Data were taken non-randomly, from the cancer registry of Cipto Mangunkusumo Hospital in 2010-2017. Data that meets the inclusion criteria, were reviewed based on data from the results of anatomical pathology examination, operating reports and laboratory examination results.

Results

Of 394 cases of epithelial ovarian cancer in Cipto Mangunkusumo Hospital from 2010-2017, 123 medical cases were not obtained, 190 exclusion cases, and 81 inclusion cases. The clinicopathological factors that had a relationship with metastasis in the omentum were serous and mucous histology, omentum nodules, and CA 125 levels. Serous type had an association with metastasis in the omentum with clear cells as a reference (OR 10.7 CI 95% 24.1-47.7; p=0.002). The mucinous type also had a significant relationship with metastasis in the omentum with clear cells as a reference (OR 14.5, CI 95% 2.5-82.2; p=0.002). We also found significant association between omental nodules and omental metastasis (OR 61, CI 95% 11.4-324.8; p<0.01). After merging cells, with categories of CA 125> 500 U / ml and CA125≤500 U / ml levels, bivariate analysis was performed with chi-square test, the results met the requirements and obtained a significant relationship (OR 3.5, CI 95% 1.2-9.7; p=0.013).

Multivariate analysis demonstrated significant association between omental nodules with metastases in omentum (aOR 40.9, CI 95% 6.6-251.9; p<0.01) and histological types of mucinous is associated with the presence of omental metastases (aOR 9.71, CI 95% 1.11-84.89; p=0.04).

Table 1. Characteristic Data.

	Frequency (n)	Percent (%)	Median (cm)
Tumor Size			20 (4,5-40)
<10 cm	9	11.1	
≥10 cm	72	88.9	
Ascites			
Yes	27	33.3	
No	54	66.7	
Omental Nodule			
Yes	11	13.6	
No	64	79	
Omental cake	6	7.4	
Histology type			
Serous	19	23.5	
Mucinous	10	12.3	
Endometrioid	20	24.7	
Clear cell	23	39.5	
Differentiation degree			
Degree 1	23	24.8	
Degree 2	22	27.2	
Degree 3	36	44.4	
Omentum metastasis			
Positive	22	27.2	
Negative	59	72.8	
Ca-125 level			245.5 (15,8-172.540)
>500U/ml	12	44.4	
35-500U/ml	9	18.8	
≤35 U/ml	1	16.7	

Table 2. Bivariate analysis of the relationship between clinicopathology factors with metastasis in omentum.

	Omental Metastasis				
	Positive	Negative	p	OR	CI 95%
Histology Type					
Serous	10 (52.6%)	9(47.4%)	0.002**	10.7	24.1-47.7
Mucinous	6 (60%)	4(40%)	0.002**	14.5	2.5-82.2
Endometrioid	3 (15%)	17(85%)	0.66**	1.7	0.3-9.4
Clear cell	3 (9.4%)	29(90.6%)	Reference	Reference	Reference
Differentiation degree					
Degree 3	12 (33.3%)	24(66.7%)	0.44*	-	-
Degree 2	4 (18.2%)	18(81.8%)			
Degree 1	6 (26.1%)	17(73.9%)			
Tumor size					
≥10 cm	18 (24.7%)	55(75.3%)	0.203**	0.32	0.07-1.44
< 10 cm	4 (50.0%)	4 (50.0%)			
Omental nodule					
Yes	15 (88.2%)	2(11.8%)	0.00**	61.0	11.4-324.8
No	7 (10.9%)	57 (89.1%)			
Ascites					
Yes	11 (40.7%)	16(59.3%)	0.052*	2.6	0.9-7.40
No	11 (20.4%)	43 (79.6%)			
CA 125 level					
>500 U/ml	12 (44.4%)	15(55.6%)	0.013*	3.5	1.2-9.7
≤500 U/ml	10 (18.5%)	44(81.5%)			

*Chi-square test
**Fisher's exact test

Table 3. Bivariate analysis of the relationship between clinicopathology factors with metastasis in omentum.

	Omental Metastasis		
	Positive	Negative	P
Tumor size (cm)	18.5(4.5-35)	20 (6-40)	0.23***
CA 125 (U/ml)	465.5 (43-6656)	212.1 (15.8-172540)	0.013***

***Mann whitney test

Discussion

In this study, the most histological types in which omental metastases occurred were mucinous types (N=6, 60%), followed with serous (N=10, 52.6%), endometrioid (N=3, 15%), and clear cell types (N=3, 9.4%). This is different from some previous studies on early-stage epithelial-type ovarian cancer which found that the histological type with the most occult metastasis was serous type (37.7%-40%); whereas the most histological type of metastasis to the omentum was serous type (20%-37.5%) (4, 6). Doig et al found that from the 318 cases of malignant tumours, the most histological type was serous, which was 144 cases, of which 120 cases (83%) had omental metastasis (17). This difference can be caused by the number of mucinous type samples is only 10 cases out of a total of 81 inclusion cases. While the number of other types of samples is more, the difference in this number is that fewer types of mucinous can cause the mucinous type to be impressed as a histological type that has a greater proportion of metastasis to the omentum.

Epithelial ovarian cancer originates from the ovarian surface epithelium, which is embryologically derived from the coelomic mesothelium (mesodermal epithelium); whereas, the uterus, cervix, and fallopian tubes develop from the Müllerian duct (ductus paramesonefros) (18-20). Coelomic mesothelium undergoes metaplasia which causes the development of cell differentiation into serous (similar to tubal epithelium), endometrioid (similar to endometrial epithe-

Table 4. Multivariate analysis of the relationship between clinicopathology factors with metastasis in the omentum.

		Wald	P	aOR	CI 95%	
					Lower	Upper
Histology type	Serous	1.67	0.19	3.99	0.49	32.42
	Mucinous	4.22	0.04	9.71	1.11	84.89
	Endometrioid	0.15	0.69	1.52	0.19	11.98
	Clear cell			Reference		
Omental nodule		16.02	0.00	40.92	6.64	251.96
Ca 125		0.02	0.96	1.04	0.18	5.86
Ascites		0.46	0.49	1.69	0.37	7.77

Regression logistic test

lium), clear cells (similar to endometrial epithelium), and mucinous (similar to the cervical epithelium and intestinal epithelium) (20, 21).

One hypothesis regarding the formation of epithelial ovarian tumours is in the transition region between mesothelial fallopian tubes and ovary fimbriae, which is an epithelial transition area that is susceptible to changes in malignancy, where the transition part is a source of carcinogenetic processes (18, 22). The mesothelium lining of the ovary consists of epithelium (keratin) and mesenchyme (vimentin). This structure also lines the fallopian tubes, uterus and peritoneal, pleural, and pericardium cavities (18, 19).

As previously known, the ovary is hung on the mesovarium and the tuba is hung on mesosalpinx. Mesovarium and mesosalpinx are part of the peritoneum. Tubes and ovaries are adjacent organs. Omentum is a continuation of the visceral peritoneum which starts from the major curvature of the stomach and the proximal part of the duodenum then extends downward, above the anterior surface of the intestine. Ovarian, tubes, omentum, and peritoneum are covered by mesothelium (23, 24). This can explain the reason why in the previous study, the histology type which had the most metastasis to the omentum was the serous type. The serous type resembles the tubal epithelium, where the ovary, tuba, and omentum are covered with mesothelium. Anatomically, there is a potential source of high-grade serous ovarian carcinoma, which is epithelial surface, fallopian tube epithelium, and mesothelium lining the peritoneal cavity (18).

In this study, omental metastasis was found in the highest number of third-degree epithelial ovarian cancers as much as 33.3%. This is consistent with previous studies which found that the most prevalent causes of occult metastases as well as the most numerous degrees of metastasis to the omentum were the third degree (52.6%-56% and 24%-37.5%, respectively) (4, 6). Theoretically, there is a figure of the growth of solid parts and atypical structures and cytology that are more common in the third-degree compared to the first- and second-degree (25). The insignificant association between the degree of differentiation and omental metastasis are not in line with previous findings. Several studies found that occult metastasis was associated with an increased degree differentiation of the tumour (4-6). This difference might be due to the proportion of positive metastatic omentum at each degree was not significantly different, resulting in insignificant relationship between the degree differentiation and omental metastasis. Previous studies described occult metastasis in all organs, not only in the omentum but also the peritoneum, lymph nodes, uterus and fallopian tubes, and the adhesion section; whereas, this study only described omental metastasis.

In this study, the median tumour size was 20 (4.5-40) cm. The median size of a tumour in cancer early stage was greater compared to the advanced stage (20 [6-40] vs 17 [4.5-35] cm, respectively). However, the differences are not statistically significant. This is in accordance with Horvart et al. who found that patients with early-stage ovarian cancer had a larger tumour size than those found in advanced ovarian cancer. In early stages, the average tumour size was 10.7 cm, and at an advanced stage of 4.8 cm (8). In this study, there was no association between the size of the tumour

with metastasis in the omentum. This is in accordance with Ahyan et al. which found that the size of tumours did not have a significant relationship with the occurrence of an increasing stage (p=0.9) (6). In this study, the differences of the median size of the tumour with omental metastasis positive and negative were not significant, 18 cm and 20 cm. In addition, the tumour size range in both positive and negative omental metastases was not significant, 4.5-35 cm and 6-40 cm.

In this study, there were 15 cases (88.2%) with omental nodules and positive omental metastases; whereas there were 57 cases (89.1%) with negative omental nodules and negative omental metastases. It is concluded that a macroscopic impression according to the microscopic impression. This is in line with a study by Usubutun et al. which found that the macroscopic impression was in accordance with the microscopic impression of 97.3% (5, 26). Doig et al. found that the impression of macroscopic is in accordance with the microscopic impression in 97.1% of cases, with PPV of 98.4% and NPV of 88% (17).

In this study, there was no correlation between ascites and omental metastasis. This is in contrast with several studies that found a correlation between the presence of ascites and more advanced stage as well as occult metastasis in early-stage ovarian cancer (4, 6). One of the metastatic pathways in ovarian cancer, is intraperitoneal metastasis (21). The ovary contacts with the peritoneum through the mesovarium, where the mesovarium is part of the mesentery. The mesentery and the omentum are parts of the peritoneum (24). Ascites, which found in the peritoneal cavity, is a medium where cancer cells will be present in the ascitic fluid. Because the capsules of ovarian tumours are disrupted, malignant cells spread to the peritoneal cavity, cells that survive can be single cells or multicellular aggregates which free-floating, called spheroids. This spheroid attaches to the extracellular mesothelial matrix, which allows it to attach as a secondary lesion to other pelvic organs, including the omentum (18, 27). In this study there was no association between ascites in the presence of metastasis in the omentum because the proportion of ascites with metastasis in the omentum was 40.7%.

According to previous studies by Ahyan et al., there was a relationship between CA 125 levels with more advanced stage in early-stage ovarian cancer (p<0.001) (6) CA125 is expressed by coelomic epithelium and tissue in adults originating from coelomic (mesothelial pleural, pericardial and peritoneal cells) and Mullerian epithelium (tube, endometrium, and endocervix) (28). CA125 is expressed as a membrane-bound protein on the surface of a cell that undergoes metaplastic differentiation into a müllerian type epithelium, or released in the form of a solution in body fluid (29). CA 125 also plays a role in cancer cell migration, and serum levels can predict metastasis (30).

After adjusting for clinicopathological factors by multivariate analysis, we found that the mucinous type had a relationship with metastasis in the omentum (aOR 9.71, 95% CI 95% 1.11-84.89; p=0.04) and the omental nodule had a relationship with omental metastasis (aOR 40.92, CI 95% 6.64-251.96; p<0.01). Whereas for the CA 125 level, there was no meaningful relationship. Soto et al. also stated that there was no relationship between CA 125 levels and occult metastases (4).

This is the first study that investigates the relationship between clinicopathologic factors with metastasis in omentum in epithelial type ovarian cancer. Several previous studies have assessed the relationship between several clinicopathological factors with occult metastases; however, they only used epithelial type ovarian cancer populations at an early stage. This study can be used as a preliminary study to provide descriptive characteristics of epithelial type ovarian cancer at Cipto Mangunkusumo Hospital. This study is limited by the small number of the subjects, as ovarian cancer cases referred to Cipto Mangunkusumo Hospital are often cases with advanced stages; therefore, many of these patients have undergone neoadjuvant chemotherapy before surgery, or they already underwent surgery in other hospitals. Thus, intraoperative data were often difficult to obtain.

Conclusions

We found that the incidence of omental metastasis in epithelial ovarian cancer is higher in mucinous histological types of and omental nodules only. Further prospective studies with larger samples are required to evaluate this relationship better. In addition, the co-

hort design can determine the causal relationship between clinicopathological factors with metastasis in omentum in epithelial type ovarian cancer.

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Increased risk of cancer and heart diseases due to the exposure to the radar EMF among the population of Potenza Picena, Italy (1986-91)

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Summary. *Background and aim of the work*: This study investigates the possible association between the prevalence of some chronic and lethal diseases in the population and the exposure to the EMF radiation of the military radar ARGOS 10, that had been located since 1970 until 1998 in the hamlet of Casette Antonelli, Potenza Picena (MC), Italy. *Methods:* Five types of diseases were researched in the hospital admissions between 1986 and 1991: cancer, heart attacks and strokes, miscarriages, congenital malformations and severe behavioral disorders. The search for such diseases was performed among 756 hospital admissions, 355 of which were for cancer and 189 for heart attack and stroke. For each observed case the address of residence was identified and the corresponding level of exposure to the radar EMF radiation was evaluated, in order to collect a large sample of data suitable to a statistical analysis based on risk indices. *Results*: The exposure to the radar radiofrequency emissions can increase the risk of cancer and heart diseases. *Conclusions:* For all the pathologies considered, the observed rate results always higher in exposed groups, since both the indices RR and OR are higher than one. In particular, the risk of cancer results to be highly significant in both patterns of comparison. For the risk of heart attack the comparison between exposed and fully exposed people is highly significant, being consistent with previous studies concluding that chronic RF exposure can bring about increased cardiovascular risk (Bortkiewicz A et al, 1995, 1996; Vangelova K et al, 2006).

Key words: electromagnetic fields, radar, epidemiology, cancer risk, heart attack risk, rate ratio, odds ratio

Introduction

The studies of the adverse effects of the exposure to radars radiation date back to the '50s when various forms of leukaemia and other blood diseases were found among men (30-40 years old) who had worked regularly with radar equipment (Daily 1943, McLaughlin 1953, 1957).

Successively, neurological effects of radar radiation were found in the foreign service and other employees of selected eastern European posts, such as the US embassy in Moscow, where there was a chronic irradiation by a Soviet radar in the years 1958-1988 (Lilienfeld et al. 1978). Hjollund (1997) reported damages on semen of personnel operating military radar equipments. Garaj-Vrhovac (2011) found a cytogenetic damage and oxidative stress on personnel exposed to marine radar equipments.

In the '90s more detailed epidemiological surveys were conducted and possible outcomes of chronic exposure to radar radiation: 1) blood count changes, 2) evidence of somatic mutation, 3) impairment of reproductive outcomes were found, especially increased spontaneous abortion, and 4) increase in cancer incidence and mortality, especially of the hematopoietic system, brain, and breast (Goldsmith 1995, 1997).

Moreover, Szmigielski (1996) and Richter (2000) reported cancer morbidity in radar technicians exposed to radiofrequency/microwave radiation.

The present study is based on the hospitals records of Potenza Picena in the period 1986-91 with a special focus on the diseases potentially related to the exposure to electromagnetic fields. The analysis considered only the records of the residents living in areas exposed to the radar EMF radiation. The results were compared to the hospital admissions regarding Potenza Picena residents not directly exposed to the radar.

Methods

Technical characteristics of the radar

The military base of Potenza Picena was established in April, 12 1956. The radar was placed on top of the hill on the edge of the coastal town in a position that could offer control of most national air space. Then, in 1972 the base was integrated into the chain of NATO Air Defence.

The radar object of our study was "Argos 10" built by Selenia. It was installed at "14th Squadron Aeronautica Militare Potenza Picena" and it had the following characteristics (source: prot. N. SMA/622/1489/t6-3/4 date 13/06/1990):

- Frequency 1000 - 2000 MHz
- Exposure time 43 ms per round
- Impulse 14
- Time of impulse 6 micro sec
- Antenna turn 12 s (5 turns per min)
- High slm 135 m
- High antenna 14,85 m
- Antenna Type ML/G 14
- Dimensions 12,9 x 6,3 m

Other characteristics by DIPIA/ISPESL (DIPIA n. 34 23/01/1991)

- Power density per impulse 20 MW
- Antenna Gain 40 dB
- Horizontal irradiation amplitude at -3dB: 1.16 degrees
- Vertical irradiation amplitude at -3 dB: 2.38 degrees

Collecting patient's data

Five types of diseases were researched in the hospital admissions between 1986 and 1991: cancer, heart attacks and strokes, miscarriages, congenital malformations and severe behavioral disorders. The search for such diseases was performed among 756 hospital admissions, 355 of which were for cancer and 189 for heart attack and stroke, 56 for miscarriage risk,50 for birth defects risks and 97 for severe behavioral disorders. For each observed case the address of residence was identified and the corresponding level of exposure to the radar EMF radiation was evaluated, in order to collect a large sample of data suitable to a statistical analysis based on risk indices.

Classification of the radar exposure according to orientation and altitude above sea level

The observed cases were classified according the exposure level to the radar radiation, following a criterion based on the home position of the patients.

In order to do so, the following data were considered:

- incidence and location of different diseases, street by street, in the years 1986-91;
- identification of the morbidity to each street and square in the town related to the level of exposure to the radar, identifying four different levels.
- Municipal census of the citizens of streets or squares (annual). The number of the exposed population was estimated as the half-sum of the starting data and the data at end of the observed period.
- The data records, including address information, come from the hospital database of Potenza Picena.

In particular, all the streets and squares of Potenza Picena have been classified, with the aid of a working group of the Tribunale della Salute of Potenza Picena, into four categories, depending on the level of exposure to the EMFs emitted by the radar. Since the altitude of the radar is 140 m a.s.l., the vertical amplitude of the signal is 2°38' (at -3 dB), and the distance from the town center is 4 km, the sector which receives

the radar emission corresponds to the range of altitude from 80 to 200 m a.s.l.; therefore, four categories of exposure were classified:

- A. unexposed (control population);
- B. slightly exposed, living near the radar (<4.5 km), at an altitude at which the level of exposure is reduced (less than 80 m or above 200m);
- C. markedly exposed, facing the radar at a distance <4.5 km, at an altitude at which the level of exposure increases (80-120 or 160-200 m);
- D. fully exposed to the radar EMF because of their altitude and orientation (120-60 m).

People living in some streets were classified in two categories (for example: 50% A and 50% C). People classified in the category D were considered to be the most exposed because the highest intensity of electromagnetic field was measured in the houses placed at the same altitude of the radar. See Table 1 which represents the pattern of people classification into categories:

The total population under study was composed by 6878 people, classified this way: 4712 (68.5%) resulted to be "not exposed" (cat. A), 856 (12.4%) resulted to be "partially exposed" (cat. B and C) and finally, 1310 (19.0%) were "fully exposed" (cat. D)

Statistical analysis of health risks

The statistical comparisons were performed according to two criteria: A vs. B, C, D (comparison between the non-exposed and exposed population) and A vs. D (comparison between non-exposed and fully exposed population). The most evident results came out from the second type of comparison.

For each type of comparison and for each one of the diseases analyzed, a contingency table was made,

Table 1. Categories of people exposure.

Residence altitude	Facing the radar	
	YES	NO
Less than 80 m	B	A
80 - 120 m	C	A
120 - 160 m	D	A
160 - 200 m	C	A
More than 200 m	B	A

Classification of the exposure to the radar signal, depending on the position of the residence of the patients

Table 2. Exposure/affection

	affected	unaffected	Total
exposed to the risk	n_a	n_b	$= n_a + n_b$
not exposed	n_c	n_d	$= n_c + n_d$
Total	$n_a + n_c$	$n_b + n_d$	$= n$

Contingency table

(see Table 2) ranking each sample data in four categories: exposed and affected by the disease (n_a), exposed and unaffected (n_b), unexposed and affected (n_c) unexposed and unaffected (n_d). Denoting by n the total number of the data, the table can be represented as in Table 2.

If there is a causal relationship between the exposure to the risk and the considered disease, (see Table 2) the values n_a and n_d (exposed patients and non-exposed healthy cases) will tend to be higher than the values n_b and n_c (exposed healthy cases and non-exposed patients). Among the most used risk indicators for data classified in this way, there are the risk ratio (Rate Ratio, RR) and the relationship of inequality (odds ratio, OR), defined as follows.

$$RR = \frac{\frac{a}{a+b}}{\frac{c}{c+d}}, \qquad OR = \frac{a/b}{c/d} = \frac{a\,d}{b\,c}$$

Using the risk ratio RR it is possible to compare directly the fraction of affected individuals among the exposed and the non-exposed population, while using the odds ratio it possible to compare the prevalence of the main diagonal values (n_a and n_d), that shows the causal link between the exposure to the risk and the disease, compared to those of the secondary diagonal (n_b and n_c), which goes to the opposite direction. If there is no causal relationship between the exposure factor and the pathology, both the indices take a value equal or close to 1, while if there is a strong causal link the two indexes tend to assume values sensibly greater than 1.

In addition to measuring the values of the indices, it is useful to apply a simple statistic test for the OR, using the normal distribution approximated by the

LOR statistic = ln OR (ln = logarithm in base e). The statistics, for the logarithms properties, can be written in the form:

$$LOR = \ln (n_a \times n_d / n_b \times n_c) = \ln n_a + \ln n_d - \ln n_b - \ln n_c.$$

Suppose that the probability of having a certain disease is P_E for exposed people, and P_N for not exposed people. The null hypothesis of the test is H_0: $P_E = P_N$. If the number of observations is not too reduced, and this condition always holds in the present study, the statistic:

$$z = \frac{LOR}{\sqrt{\frac{1}{n_a} + \frac{1}{n_b} + \frac{1}{n_c} + \frac{1}{n_d}}}$$

follows, under the null hypothesis H_0, a standard normal distribution N(0,1). Therefore, if the observed value of z is a tail value of the standardized normal variable, the null hypothesis is rejected and, indeed, an effect of the risk factors on the probability of occurrence of the considered disease becomes plausible. The p-value corresponds to the probability of obtaining, only due to random effects, a result equivalent or more extreme than the one effectively observed.

If the p-value is less than 5% (1/20), the result is considered significant. If it is less than 1% (1/100), it is considered highly significant. The Tables 3 to 12 represent the main results obtained in this study; the p-value is displayed for each comparison, and Statistical Significance it is specified with the initials S. for Significant and N.S. for not Significant Also a 95% confidence interval for the parameter is given, i.e. a range of values that contains, with a probability of 0.95, the "true" value of the index in the population.

Results

For all the pathologies considered, the observed rate is always higher in exposed groups, since both the indices RR and OR are higher than one. In particular, the risk of cancer results (Tables 3 and 4) to be highly significant in both patterns of comparison (exposed/

Table 3 - Risk of Cancer: Comparison A (not exposed) vs. B, C, D (exposed)

	Affected	Not affected	Total
Exposed	139	2027	2166
Not exposed	216	4496	4712
Total	355	6523	6878
RR =	1,400		
OR =	1,427	(1.208 - 1.647)	
z =	3,177		
p value	0,074%	(1/3144) S.	

S.= Statistically Significant
Rate ratio and odds ratio calculation for the cancer risk between exposed and not exposed patients.

Table 4 - Risk of Cancer: Comparison A (not exposed) vs. B, C, D (exposed)

	Affected	Not affected	Total
Exposed	139	2027	2166
Not exposed	216	4496	4712
Total	355	6523	6878
RR =	1,400		
OR =	1,427	(1.208 - 1.647)	
z =	3,177		
p value	0,074%	(1/3144) S.	

S.= Statistically Significant
Rate ratio and odds ratio calculation for the cancer risk between exposed and not exposed patients.

Table 5 - Risk of heart attacks and strokes: Comparison A (not exposed) vs. B, C, D (exposed)

	Affected	Not affected	Total
Exposed	69	2097	2166
Not exposed	120	4592	4712
Total	189	6689	6878
RR =	1,251		
OR =	1,259	(0.959 - 1.560)	
z =	1,502		
p value	6,65	(1/15) N.S.	

N.S. = Not Significant
Rate ratio and odds ratio calculation for the heart attack and stroke risk between exposed and not exposed patients.

Table 6 - Risk of heart attacks and strokes: Comparison A (not exposed) vs. D (fully exposed)

	Affected	Not affected	Total
Exposed	54	1256	1310
Not exposed	120	4592	4712
Total	174	5848	6022
RR =	1,619		
OR =	1,645	(0.959 - 1.560)	
z =	2,984		
p value	0,142%	(1/15) N.S.	

S.= Statistically Significant
Rate ratio and odds ratio calculation for the heart attack and stroke risk between fully-exposed and not exposed patients

Table 7 - Risk of miscarriages: comparison A (not exposed) vs. B, C, D (exposed)

	Affected	Not affected	Total
Exposed	21	2145	2166
Not exposed	44	4668	4712
Total	65	6813	6878
RR =	1,038	(0.515 - 1.561)	
OR =	1,039		
z =	0,142		
p value	44,35%	(>5%) N.S.	

N.S. = not significant
Rate ratio and odds ratio calculation for miscarriage risk between fully-exposed and not exposed patients

Table 8 - Risk of miscarriages: comparison A (not exposed) vs. D (fully exposed)

	Affected	Not affected	Total
Fully exposed	16	1294	1310
Not exposed	44	4668	4712
Total	60	5962	6022
RR =	1,308	(0.736 - 1.887)	
OR =	1,312		
z =	0,923		
p value	17,80%	(>5%) N.S.	

N.S. = not significant
Rate ratio and odds ratio calculation for miscarriage risk between fully-exposed and not exposed patients

Table 9 - Risk of birth defects: comparison A (not exposed) vs. B, C, D (exposed)

	Affected	Not affected	Total
Exposed	18	2148	2166
Not exposed	32	4680	4712
Total	50	6828	6878
RR =	1,244	(0.649 - 1.805)	
OR =	1,226		
z =	0,688		
p value	24,57%	(>5%) N.S.	

N.S. = not significant
Rate ratio and odds ratio calculation for birth defects risk between exposed and not exposed patients.

Table 10 - Risk of birth defects: comparison A (not exposed) vs. D (fully exposed)

	Affected	Not affected	Total
Fully exposed	13	1297	1310
Not exposed	32	4680	4712
Total	45	5977	6022
RR =	1,461	(0.818 - 2.113)	
OR =	1,466		
z =	1,160		
p value	12,30%	(>5%) N.S.	

N.S. = not significant
Rate ratio and odds ratio calculation for birth defects risk between fully-exposed and not exposed patients.

Table 11 - Risk of severe behavioral disorders: comparison A (not exposed) vs. B, C, D (exposed)

	Affected	Not affected	Total
Exposed	36	2130	2166
Not exposed	61	4651	4712
Total	97	6781	6878
RR =	1,284	(0.874 - 1.704)	
OR =	1,289		
z =	1,055		
p value	14,57%	(>5%) N.S.	

N.S. = not significant
Rate ratio and odds ratio calculation for behavioral disorders risk between exposed and not exposed patients.

Table 12 - Risk of severe behavioral disorders: comparison A (not exposed) vs. D (fully exposed)

	Affected	Not affected	Total
Fully exposed	22	1288	1310
Not exposed	61	4651	4712
Total	83	5939	6022
RR =	1,297	(0.811 - 1.794)	
OR =	1,302		
z =	1,198		
p value	11,55%	(>5%) N.S.	

N.S. = not significant
Rate ratio and odds ratio calculation for behavioral disorders risk between fully-exposed and not exposed patients.

not exposed and fully exposed/not exposed), as shown in Table 3, 4. Regarding the risk of heart attack (Tables 5 and 6), the comparison between fully exposed and not exposed is highly significant, as shown in Table 4.while the comparison between exposed and not exposed people is not significant but near to the statistical limit. For the other pathologies considered (miscarriages, birth defects and severe behavioral disorders) the results are not significant, but the indices of risk are always higher in the second kind of comparison (fully exposed/not exposed), as can be seen in Tables from 7 to 12.

Discussion

According to the results obtained for the different pathologies, it has been found that the comparison between exposed and unexposed (A vs. B C D) is highly significant for cancers (with a frequency higher than 40% among the exposed) and very close to the threshold of significance for heart attacks and strokes (frequency higher than 25% of the exposed). The comparison between the unexposed and the highest level of exposure (A vs. D) is significant both for the tumors (+ 50% among the exposed) and for heart attacks and strokes (+ 61% among the exposed). Taking into account multiple comparisons, the significant comparisons remain valid also when applying Bonferroni correction, which is very conservative for the null hypothesis, consisting in multiplying the p value for the number of tests carried out (in this case 5, one for each pathology).

Therefore, the higher exposure areas, and in particular the zone D (the fully exposed town zone) show significantly higher incidences of tumors and heart attacks, when compared to the less exposed areas. The percentage increases observed in zone D (most exposed category) than non-exposed are 61% for heart attacks and stroke and 50% for tumors. If we compare the unexposed group with the three groups exposed, the increments are 40% for cancers and 25% for heart attacks and strokes.

For the other pathologies the found differences resulted to be far from significance limit, even if the inhabitants of the exposed areas are in any case more affected than others, and the difference is systematically more relevant when comparing fully exposed with not exposed. The lack of significance for the last three pathologies could possibly be due not only to lower values of the risk levels, but also to the very small number of cases observed. In fact, it is well known that, at equal levels of RR and OR, the pathologies most frequently observed are the most significant.

The results obtained can give a preliminary answer to the problem of determining the effect of electromagnetic radiation on human health. Actually, the findings suggest a correlation between the radar emissions and some major diseases such as heart attacks, strokes and cancers. The analysis, carried out on the basis of information that was available to the authors, should be updated and conducted more in-depth, for example, by focusing the various types of cancer, identifying the locations where the diseases are localized and eventually causing an increase in mortality. It would be very important to make an overall meta-analysis, comparing and integrating the results considering various areas exposed to strong electromagnetic emissions.

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Cutaneous metastases from lung adenocarcinoma: a case report

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Summary. Cutaneous metastases from lung carcinoma are rare and have ominous prognosis. They are an important finding and are not often the first sign leading to diagnosis. We reported a case in which a 52-year-old male, smoker, initially presented with rapidly growing skin nodules on his back and right thigh, without any pulmonary complaints. Biopsy of the skin nodules revealed metastatic adenocarcinoma consistent with primary lung origin. Computed tomography showed an expansive process on the upper lobe of left lung with atypical characteristics suspicious of primary site. Abdominal and pelvic CT scan showed disseminated bone metastases. In a multidisciplinary discussion, it was considered that there is no indication for chemotherapy or radiotherapy due to the rapid clinical worsening of the patient. He received palliative treatment and died 5 weeks after diagnosis of his metastatic lung cancer. We are presenting a rare case of lung adenocarcinoma with skin metastases, which was simultaneously diagnosed. A high index of suspicion is necessary for the early detection of cutaneous metastases from lung tumours, especially if there is history of smoking or lung cancer.

Key words: cutaneous metastases, lung cancer, adenocarcinoma

Introduction

Cutaneous metastatic disease is uncommon, ranging from 1 to 12% and may represent the first manifestation of an internal, asymptomatic or unsuspected, occult malignancy (1-3).

Lung cancer has become one of the most common type of malignancy with high mortality rate (4). The most common histological type is adenocarcinoma, followed by squamous cell carcinoma, small cell carcinoma, large cell carcinoma, and bronchial carcinoid. It frequently metastasizes to liver, hilar lymph nodes, contralateral lung, adrenal glands, bone and brain (5), while the skin is rarely affected (6). All histological types of lung cancer may metastasize to the skin and clinical lesions are variable. Most common sites of skin metastases from lung cancer are the anterior chest, abdomen, head and neck. Although, they do not have a characteristic clinical presentation, they are often described as round or oval nodules, mobile or fixed, hard or flexible, single or multiple (usually grouped), and skin-coloured (but sometimes flesh-coloured, red, pink, purple, or bluish black) (6). The nodules are usually painless but they may ulcerate or necrotize. The presence of skin metastases from lung cancer is associated with poor prognosis (5).

We hereby present a case of lung adenocarcinoma with skin metastases, which was simultaneously diagnosed.

Case Presentation

A 52-years-old caucasian male, heavy smoker, with a past medical history of dyslipidemia and Peyronie's Disease, was admitted at the emergency department with lower back pain upon injury, with a three weeks extent, refractory to conventional pain treatment and with high functional incapacity. The patient also reported the onset of multiple skin nodules, with rapid

growing, located in the back, right thigh and close to the xiphoid process with an evolution of two months. The nodules were firm, tender, skin-coloured, painless and measured 5-15 millimetres in greatest dimension. The nodule from right thigh evolved to ulcer after treatment with topic antibiotic (Figure 1). In addition, the patient exhibited signs of weight loss, anorexia and dysphonia but no respiratory symptoms. On physical examination there was a large, ulcerative, well-circumscribed lesion, measuring 35 mm in diameter on the on right thigh, and multiple subcutaneous nodules, firm, tender and painless on abdominal wall, back and chest with no cervical, axillary and inguinal lymphadenopathy. The remainder of the exam was normal. Laboratory results were within normal. Lumbar Computed tomography (CT) scan revealed an osteolytic lesion on vertebral body of L2 and S2 suspicious of secondary deposits. Lumbar spine magnetic resonance imaging (MRI) exhibited multiple lesions on vertebral bodies and posterior arches of D9, D11, D12, L2, L3 and L4, sacrum and wings of ilium suspicious of metastatic deposits (Figure 2).

The patient was admitted to the Medicine ward for further investigation. Excisional biopsies were performed to the ulcerative lesion of the thigh and one of the lesions of abdominal wall. Histopathology confirmed metastatic nature of the lesions (Figure 3) namely adenocarcinoma with solid pattern, poor differentiated,

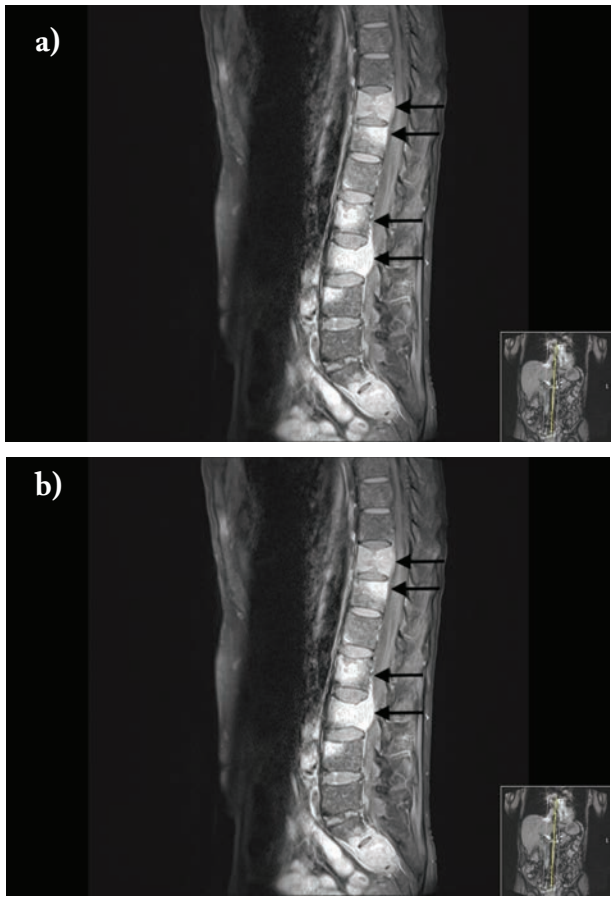

Figure 2. Magnet resonance imaging of metastases located in the axial skeleton, spine and pelvis.

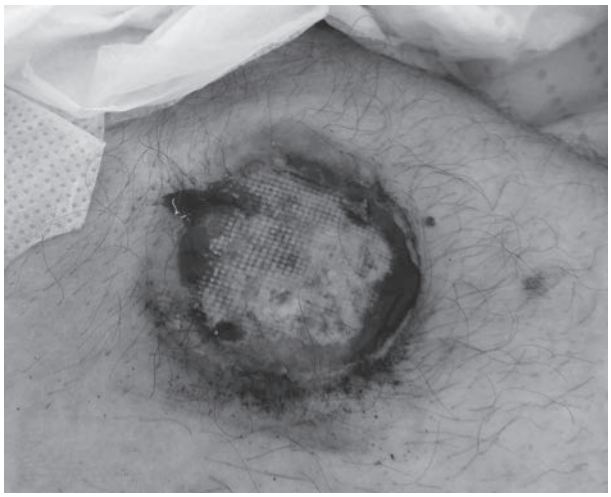

Figure 1. Macroscopic aspect of the ulcerate skin lesion from right thigh.

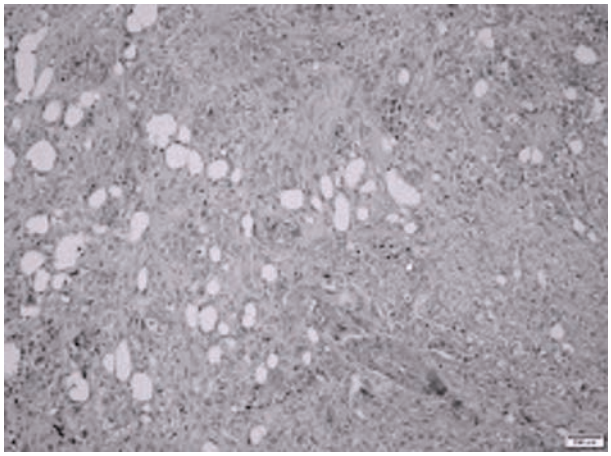

Figure 3. Hematoxylin & eosin stain: ulceration of the epidermis with infiltration by adenocarcinoma.

favouring pulmonary origin. In immunohistochemistry, tumour cells were positive to Cytokeratin 7 (CK-7) (Figure 4) and there was no expression of Cytokeratin 20, Cytokeratin 5/6, estrogen receptors, prostate specific antigen (PSA) and thyroid transcription factor 1 (TTF-1) (not shown). For further evaluation, chest CT scan revealed an expansive process in the upper lobe of left lung with atypical characteristics accompanied by closure of the superior lobar bronchus with vascular invasion (Figure 5), bilateral pleural effusion and two nodular lesions in the left lung- one parenchymal and other pleural - and two sub-pleural nodules on the right lung attributable to metastases. Abdominal and pelvic CT scan showed disseminated bone metastases especially in the axial skeleton, spine and pelvis. Head CT was normal. Because of dysphonia, patient was observed by the otolaryngology and it was identified paralysis of the left hemilarynx by probable compression of the left recurrent laryngeal nerve at the thoracic level due to pulmonary nodular lesion. A bronchoscopy was planned, but during his hospital stay, the patient developed a bronchopneumonia, and his condition worsened rapidly with degradation of his clinical status, and he was not fit to perform the procedure.

The clinical case was evaluated in a multidisciplinary discussion and it was considered that patient did not present clinical conditions to start chemotherapy or radiotherapy. Therefore, he received received supportive therapy, mainly pain treatment by palliative care team. It was observed an unfavourable clinical course and patient died 5 weeks after lung cancer diagnosis. Skin metastases were the first sign.

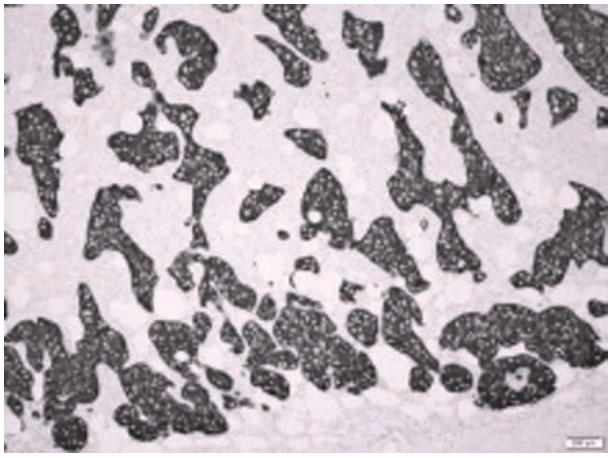

Figure 4. Positive Cytokeratine 7 immunostaining.

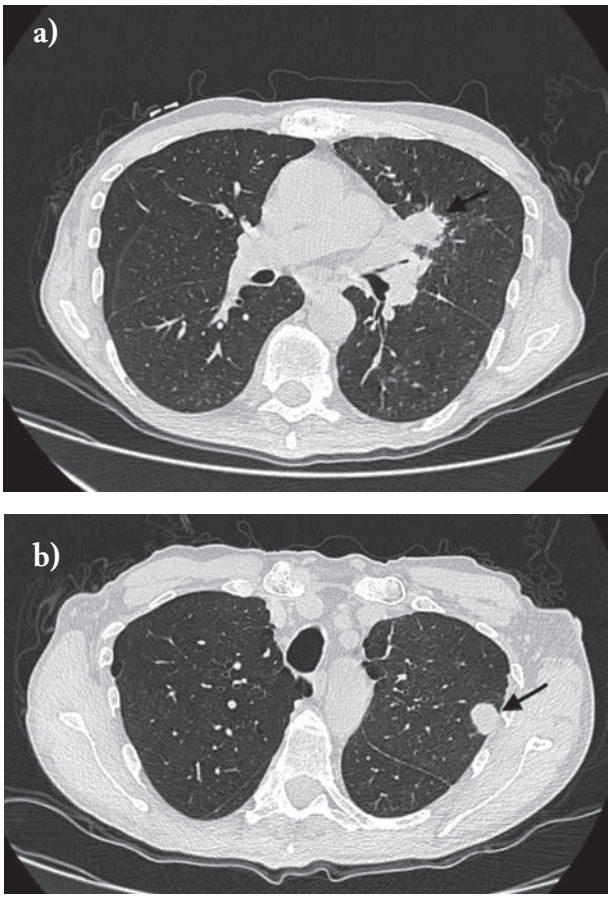

Figure 5. Computed tomography revealed a solid expansive process in the upper lobe of the left lung.

Discussion

Cutaneous metastases of lung cancer are rare and according to some data, they are more frequent in men then in women (6). Although, its low incidence it is important to ruled out in patients with suspicious skin lesions, history of lung carcinoma, or tobacco exposure. Our patient was male, had a history of heavy smoking, and had multiple cutaneous lesions as the first presentation for an underlying undiagnosed lung adenocarcinoma.

Most skin metastases occur in regions close to the primary cancer, however lung, melanoma, and breast

malignancies are the cancers most likely to metastasize to remote cutaneous sites (7). The most common sites of lung skin metastases are the scalp, head and neck region, and the anterior chest in men and the anterior chest wall and the abdomen in women, with the most histological diagnosis, in both gender, being adenocarcinoma (8). In 20-60% of reported cases, the skin lesions may present before or concurrently with the diagnosis of primary tumor (1, 3, 6). In this case, the histological type was adenocarcinoma with skin lesions presented in the back, right tight, chest and abdominal wall, however no lesions in the scalp or head/neck were found. These lesions grew fast over a 2 months period, before the first occurrence of his bone complaints (due to bone metastases) and no pulmonary symptoms were reported until the presence of pulmonary infection.

Physically, cutaneous metastatic lesions due to lung cancer are indistinguishable from those due to carcinoma originating elsewhere in the body, nevertheless nodular lesions, often multiple, are the most frequent ones (9). Histologically, skin metastases from the lung are frequently poor differentiated and immunohistochemical markers that may be useful for diagnosis are TTF-1, CK-7 and CK-20 (10, 11)and cytokeratin 7 (CK7. However, if there is unknown primary site, further investigations should be done by history, physical exam, and multiple imaging methods. Nevertheless, being the first sign of presentation, cutaneous metastases biopsy can often help find the primary cancer, since the primary lung lesion often remains quiescent, such as in our case. For our diagnosis, two nodular subepidermal specimens were stained with CK-7, which is specific to adenocarcinoma. In this case, excisional biopsy of the primary lung lesion was not performed but imaging revealed a nodular lesion with atypical characteristics; thus combining those imaging and histological findings with the patient's heavy smoking history, the diagnosis of lung adenocarcinoma was made.

The presence of cutaneous metastases in lung cancer has a poor prognosis and short survival, as they demonstrate that the primary cancer is advanced. Patients that present with skin metastases earlier during the disease course, have poorer prognosis compared to those with later developed metastases. Other poor prognostic indicators include small-cell primary lung tumours (nonresectable), multiple metastatic cutaneous lesions, and/or other distant metastases (12, 13). Our patient had three poor prognostic indicators: skin lesion presented before lung cancer diagnosis, multiple cutaneous metastases and other distant metastases (bone, pleural and contralateral lung secondary deposits). The median survival is approximately 3 months in patients with skin and organ metastasis, whereas the survival reaches 10 months in patients with only skin metastasis (12). Our patient survived only 5 weeks after the time of diagnosis.

Although it is uncommon, cutaneous metastases, which may be concurrent with the diagnosis of lung cancer, may be the first sign of the disease. Due to the non-specific appearance, they can be misdiagnosed as benign lesions. Therefore, it should be suspected in cases of atypical lesions in the skin of smokers.

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Retroperitoneal extrarenal angiomyolipoma: how to differentiate it from retroperitoneal liposarcoma with a case report

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Summary. Extrarenal retroperitoneal angiomyolipomas (ERAMLs) are extremely rare benign lesions that can imitate some other benign and malignant retroperitoneal masses. In order to prevent the imposing an unnecessary debilitating treatment for these patients, recognizing its clinical characteristics (including imaging features) matters a lot. We present a very rare case with ERAML to shed light, especially on its radiological attributes. We proposed a pair of radiologic findings that may have the potential to differentiate ERAML from its malignant differential diagnosis (i.e. retroperitoneal liposarcoma) that are intratumoral aneurysmal vessels and intratumoral hemorrhage. We presented this especial case report in hope to guide further studies to make a valuable clinical blueprint to differentiate ERAML from retroperitoneal liposarcoma.

Key words: angiomyolipoma, liposarcoma, hemorrhage, aneurysm

Introduction

Angiomyolipomas (AMLs) are benign tumors that are characterized by the presence of three distinct histological components, with varying amounts (i.e. blood vessels, fat cells and smooth muscle cells) (1). They are most commonly found in the kidneys. While extrarenal sites are also reported to harbor AML. One of these uncommon sites is retroperitoneal (RP) space. In light of its extreme rarity, the related features (including epidemiology, pathophysiology, imaging findings, etc.) are still not well defined. In this especial article, by introducing the first Iranian patient with extrarenal retroperitoneal angiomyolipoma (ERAML), we intend to shed light on its specific radiologic features to direct further studies to differentiate it from its malignant counterparts to preclude strenuous surgeries in asymptomatic patients.

Case presentation

A 29-year-old woman, without significant past medical history, was referred to the Radiation-oncology department of Shohada-e Tajrish General Hospital (Tehran, Iran) with chronic, intermittent, and dull right-sided flank pain. The abdomen was soft on examination with moderate pain during deep palpation of the right lower quadrant (RLQ) of the abdomen. With the initial impression of appendicitis, abdominopelvic ultrasonography was performed with the following report:

"There is no finding in favor of appendicitis, however a 9 cm ×6 cm × 5 cm heteroechoic mass is present at RLQ with extension to the liver".

The contrast-enhanced computed tomography confirmed a retroperitoneal mass, with mixed density appearance and areas of fat attenuation and also

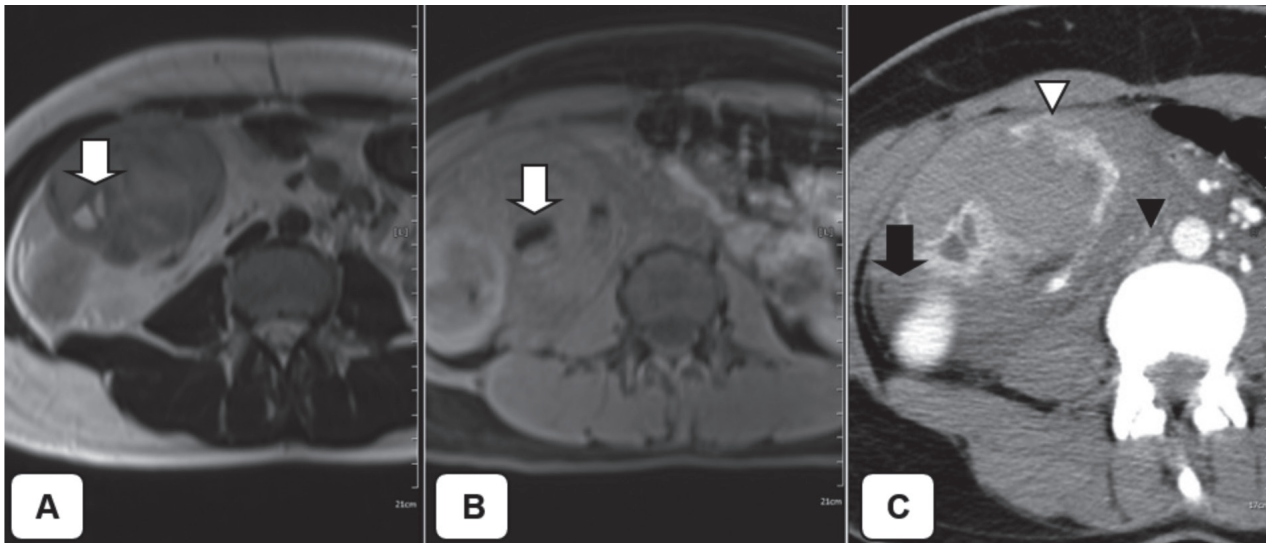

Figure 1. Transverse sections of enhanced CT scan and MRI show a well-defined, heterogeneous extra-renal retroperitoneal mass that is located at medio-lateral site of right kidney and contains a central prominent aneurysm. T1-weighted MRI (a) and T2-weighted MRI (b) show vascular aneurysm with apparent signal void feature at T2-weighted MRI (arrow). Contrast-enhanced CT scan (c) shows mixed density mass with fat attenuation and hyperdense area in accordance with hemorrhagic sites (white arrowhead) that has displaced the right kidney and IVC (black arrow and black arrowhead, respectively)

some areas of hemorrhage that has displaced the right kidney (figure 1). These findings also confirmed with MRI HASTE (Half-Fourier-Acquired-Single-shot Turbo Spin Echo) and CT chemical shift sequences (figures 2, 3).

The differential diagnosis were as follow: Retroperitoneal liposarcoma (RL) and ERAML.

Afterward, considering the impression of resectable liposarcoma, the patient underwent complete surgical resection. However, the pathology result was in favor of another suggested diagnosis (i.e. angiomyolipoma). It is noteworthy that the resection specimen contained a fragment of renal tissue that did not have any connection with AML mass. Consequently,

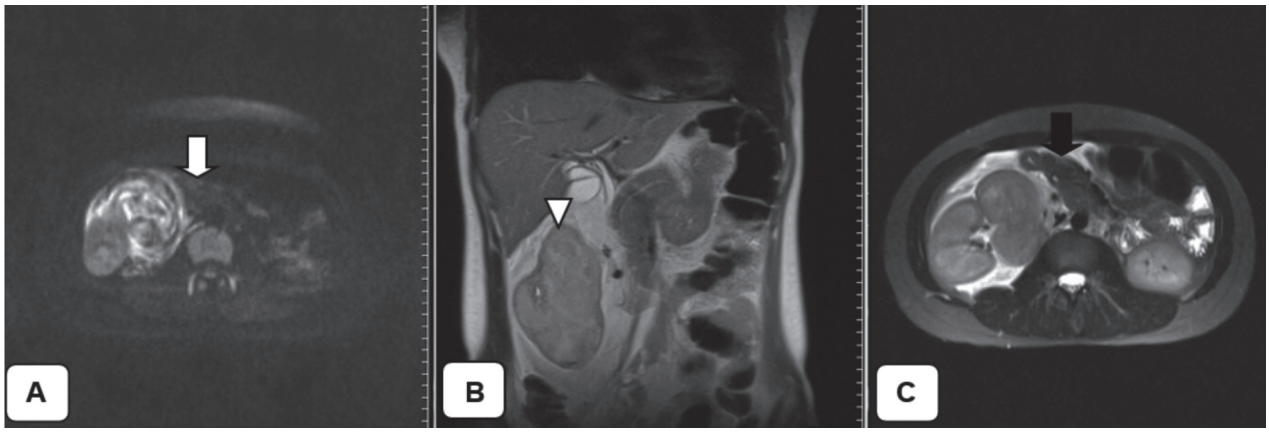

Figure 2. Three MRI sequences of the ERAML. a) Axial section of the diffusion-weighted MRI shows diffusion restriction that is in favor of hemorrhage. b) Coronal view of T1-weighted MRI that depicts well-demarcated heterogeneous mass that extends from subhepatic site to pelvic inlet. c) Half-Fourier- Acquired Single-shot Turbo Spin Echo (HASTE) sequence of the ERAML shows a well-defined mass with a hemorrhagic site.

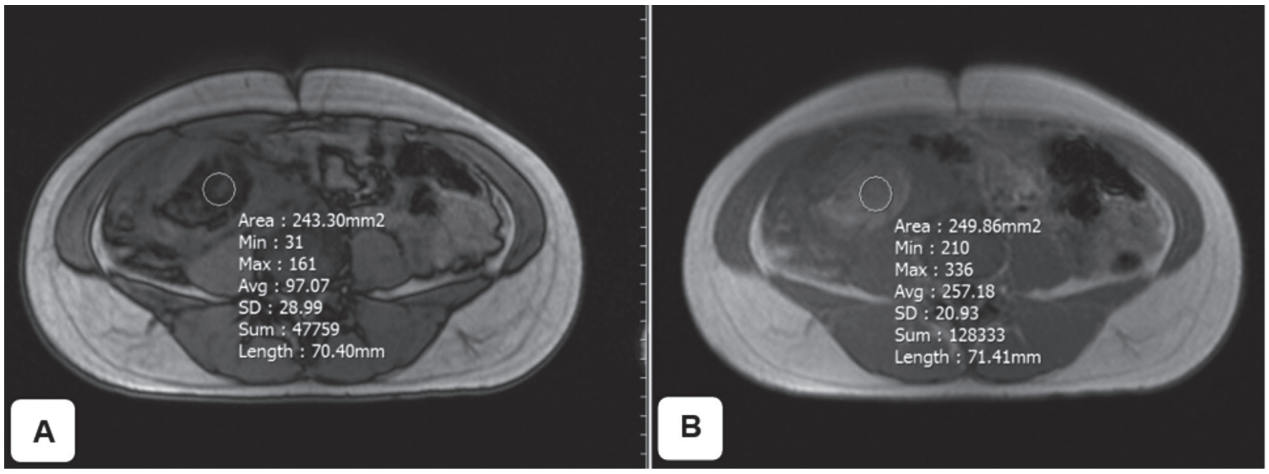

Figure 3. Chemical shift sequence. The figures show significant drop on out-of-phase image of mass. The signal intensity ratio is about 0.38 compatible with fat content of the ERAML. a) out-of-phase, b) in-phase.

the ERAML was proposed as the final diagnosis. The mass located adjacent to the right-sided kidney measured 10 cm × 6 cm × 6 cm that excised with negative surgical margins. Pathology review was done and according to positive immunohistochemistry (IHC) for HMB-45, the initial diagnosis was confirmed.

Considering the benign nature of AML and achievement of acceptable negative surgical margins, follow-up was planned for her status (with history taking, physical examination and the abdominopelvic US every six months for initial two years and after that annually until ten years).

Discussion

AMLs are benign lesions that are composed of varying amounts of three distinct mature tissues (i.e. adipose tissue, dysmorphic blood vessels with spindle and epithelioid cells). They commonly arise within the kidneys. Renal AMLs have two distinct variants: classic and epithelioid (1). The epithelioid variant is categorized from the classic type by the presence of epithelioid cells (2). ERAMLs, also known as retroperitoneal angiomyolipomas (RAMLs), are uncommon retroperitoneal lesions that can imitate other retroperitoneal masses. Considering the liver as the most common extrarenal site of AMLs, RP space constitutes the second place in this perspective (3). Its incidence rate is extremely low, that based on a recent review article, only 30 cases were reported until January 2016. According to this study, it occurs predominantly in females, with a median age of 39 years. Common presentations of ERAMLs are pain (esp. on abdomen, groin, back), weight gain/loss, fullness of epigastrium, constipation, and hematuria. However, sometimes it appears incidentally, following imaging. There are some lesions that can mimic ERAML (e.g. liposarcoma, leiomyosarcoma, rhabdomyosarcoma, renal cell carcinoma). Among them, liposarcoma is more challenging to differentiate, in terms of location and histopathology (4). The distinction between ERAML and retroperitoneal liposarcoma (RL) is an important issue. Since ERAML is a benign lesion, debilitating surgical resection and radiotherapy often are not essential. On the other hand, regardless of radiologic findings, the diagnosis of ERAML may be mistaken. For example, according to the Ellingson et al study, based solely on biopsy, one out of nine AML cases was reported as liposarcoma (5).

Imaging modalities can play an essential role in differentiating ERAMLs from RLs. According to the literature review, the radiologic findings of RAMLs are characterized from RLs (Table 1) (6). Some other possible AMLs peculiarities, that can help to differentiate it from RLs, are suggested in the literature. For

Table 1. Summary of MDCT features of differentiating renal AML from RL

MDCT features	Renal AML (n=31) (%)	RL (n=11) (%)	P value
Renal parenchymal defect	31 (100)	1 (9)	0.000
Renal artery vascular supply	31 (100)	0 (0)	0.000
Tumoral vessels extending through renal parenchyma	31 (100)	0 (0)	0.000
Dilated intratumoral vessels	29 (94)	1 (9)	0.000
Hemorrhage	11 (35)	0 (0)	0.041
Non-fat-attenuating enhancing intratumoral nodules	0 (0)	9 (82)	0.000
Intratumoral calcification	0 (0)	4 (36)	0.003
Renal sinus enlargement	18 (58)	1 (9)	0.006
Anterior displacement of the kidney	10 (32)	9 (82)	0.011
Associated AML	12 (39)	0 (0)	0.018

AML: angiomyolipoma, RL: retroperitoneal liposarcoma, MDCT: multi-detector CT
Courtesy of Wang et al. "Differentiating renal AML from retroperitoneal liposarcoma", September 2015.

instance, the presence of the region of interest (ROI) with attenuation (in CT scan) less than -10 HU can depict the presence of fat cells in AML (7). Nevertheless, RL also contains fat cells. Therefore, this method seems not to be so confident.

Considering extreme rarity of ERAML, a valuable study has not yet been done regarding its radiological characteristics. Therefore, introducing potentially available key imaging features of ERAML can resolve the existing ambiguity between ERAMLs and RLs. Since it appears that ERAML originates from the extrarenal tissue, some of its radiological features possibly are different from its renal counterpart. For example, we expect "Renal artery vascular supply" not to exist in ERAML. While it is conceivably logical to extrapolate some intrinsic features of AML to ERAML (e.g. hypervascularity with the presence of aneurysmal vessels inside the tumor mass). Another finding that may be in favor of ERAML is intra/extra tumoral hemorrhage (due to the presence of intratumoral dysplastic blood vessels). However, in generalizing this issue, it has to be cautious; because in a case report intratumoral hemorrhage was reported in a patient with the diagnosis of RP liposarcoma (8). Noteworthy, among all of these characteristics there were only two features that were present in our patient (based on retrospective assessment). They are including intratumoral aneurysmal vessels and intratumoral hemorrhage (Figure 1, 2).

These findings have the potential to be a valuable clue for further studies to define the comprehensive radiological characteristics of ERAML, in hope that it would be helpful in clinically distinguish it from its malignant differential diagnosis (i.e. RL) to spare the affected patient from a radical surgery.

Contributors: Farzad Taghizadeh Hesary performed main parts of literature review and manuscript draft. Anya Jafari provided the data and edited the manuscript. Morteza Sanei Taheri provided the imaging data and edited the manuscript. All authors read and approved the final manuscript.

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Thrombotic microangiopathy as a presentation of undifferentiated metastatic carcinoma, a case report

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Summary. Thrombotic microangiopathy (TMA) is a group of hereditary or acquired syndromes that shared clinical and pathological characteristics: microvascular thrombosis, thrombocytopenia and ischaemic end-organ damage. Thrombotic microangiopathy can be a manifestation of a subjacent disease as cancer, infection, auto-immune disease and others. Patients presenting cancer-related TMA have an extremely poor prognosis. We report a case of a 61-year-old man who was admitted for persistent lumbar pain. Results from imagiological exams showed multiple retroperitoneal lymph nodes suggestive of metastatic cancer. A sudden clinical episode with changes in mental and behavioral status and laboratory alterations consistent with TMA, were observed. A first strategy including plasma exchange and steroids was performed with no clinical response. The retroperitoneal lymph node biopsy revealed undifferentiated carcinoma of unknown primary and then, chemotherapy was started.

Key words: thrombotic microangiopathy, thrombotic thrombocytopenic purpura, cancer

Introduction

Thrombotic microangiopathy (TMA) is a group of hereditary or acquired syndromes that share clinical and pathological characteristics: microvascular thrombosis, thrombocytopenia and ischaemic end-organ damage (1). Haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura (TTP) are the two major subtypes. TTP is described by a pentad with thrombocytopenia, microangiopathic haemolytic anaemia (MAHA), neurologic deficits, renal failure, and fever. This classic pentad is rarely observed and the two first symptoms are essential to diagnosis (2). TMA can be a manifestation of a subjacent disease as cancer, infection, auto-immune disease and others (1-3). TMA cancer-related is different to another causes: ADAMTS13 activity is normal and sparse response to plasma exchange occurs (1, 3).

Patients with cancer-related TMA need an urgent treatment to directed to cancer because the prognosis among these cases is extremely poor (3).

Case report

We present the case of a 61-year-old man, Caucasian, with an history of mesangioproliferative glomerulonephritis, arterial hypertension and obstructive sleep apnea, that was admitted for intense lumbar pain with 1 month of evolution and urinary symptoms, dyspepsia, night sweats and weight loss (4 kgs/1 month). Physical examination showed pain only in the lower quadrant of the abdomen. No alterations on blood analysis except reactive protein-C 11.7 mg/L (<3 mg/L). Urinalysis showed leukocyturia and proteinuria (1g/L). After, urinary culture revealed Enterobacter cloacae, ciprofloxacin-sensitive and antibiotherapy was started in a first approach. To characterize the pain, an abdominal computerized tomography (CT) was realized and showed "numerous retroperitoneal, retrocrural and celiac lymphadenopathies, being the largest with 22x17 mm". A biopsy of one lymphadenopathy was done. An upper and lower gastrointestinal endoscopy, thoracic CT, lumbar X-ray, scrotal, pelvic and prostatic ultra-

sound were performed, and no alterations were found. PSA total result was 0.240 ng/mL (<4). We excluded auto immune disease, sarcoidosis, tuberculosis, hepatitis B and C, Human Immunodeficiency Virus and other infectious diseases. Despite the treatment, the patient maintained lumbar pain. At day-19 he started with neurologic alterations (confusion, prostration and dysarthria), pallor of skin and mucous membranes. No alterations were reported in a head CT Scan. . Blood analysis showed the presence of anemia (hemoglobin 7.3 g/dL (reference values 13-18)); thrombocytopenia (platelets 88000 (150000-400000)); liver function alterations (Aspartate transaminase 75 U/L (10-37); alanine aminotransferase 97 U/L (10-37); gama glutamil transferase 84 U/L (10-49); total bilirubin 2.28 mg/dL (<1.2), direct bilirubin 0.45 mg/dL (<0.4); lactate dehydrogenase (LDH) 583 U/L (135-225); presence of schistocytes, haptoglobin <8 mg/dL (50-320), direct Coombs test negative. Therefore, a clinical diagnosis of TMA (microangiopathic hemolytic anemia, thrombocytopenia and neurologic disfunction) was stated. Plasma exchange and steroids were started. A neurological improvement with a hematological worsening was seen after 4 days of treatment. At this time, we had the result of biopsy that showed "morphological and immunohistochemical features compatible with metastasis of undifferentiated carcinoma". The discussion of the case was presented in a multidisciplinary team and it was decided to start chemotherapy with paclixel and carboplatin. The patient maintained worsening and best supportive care was performed. The patient passed away after 28 days.

Discussion

Thrombotic microangiopathy (TMA) is a group of different syndromes, hereditary or acquired, secondary to various systemic diseases, including cancer; with sudden or gradual onset; but with common clinical and pathological features. Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic Uremic Syndrome (HUS) are included. TTP is a syndrome consisting of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and organ damage secondary to microvascular thrombi. Classical pentad (MAHA, thrombocytopenia, fever, neurological and renal changes) are rarely present (5-40%) (1-3). MAHA and thrombocytopenia are universal and according to the new diagnostic criteria are those necessary for the diagnosis of PTT (3). Other situations have been reported where TMA is a manifestation of the underlying disease, such as cancer, infections, transplants, autoimmune diseases and severe hypertension (3, 4). Among the secondary causes, in the cancer-related TMA there are at least two entities: one induced by chemotherapy and another induced directly by cancer. The latter has a pathophysiology still largely unknown but different from the others TMA: tumor invasion, endothelial damage caused by abnormal growth and tumor angiogenesis. The response to plasma exchange in TMA related to cancer is sparse. The most frequently associated cancer are adenocarcinomas, essentially gastric, breast and lung. Although it may arise at an early stage, most of described cases are diagnosis in an advanced stage (4, 5).

There are no laboratory findings that confirm the TMA, and its diagnosis encompasses clinical history, physical examination and blood analyses with a peripheral blood smear (1-3). Symptoms related to thrombocytopenia such as hemorrhage and ecchymosis; neurological changes, fever and nonspecific symptoms may be present (pallor, myalgias, jaundice, fatigue; proteinuria and hematuria, abdominal pain, chest pain…). Thrombocytopenia is caused by the consumption of platelets in platelet-rich thrombi. Mechanical fragmentation of erythrocytes occurs when they pass into a partially occluded vessel, causing non-immune hemolytic anemia (presence of schistocytes in peripheral blood, decreased haptoglobin, reticulocytosis, and negative direct coombs test). The observed increase in LDH is explained by hemolysis and tissue ischemia. Coagulation tests presented normal values (1-5). In the case we report, patient was admitted for retroperitoneal adenopathies, probably as a result of metastases of an occult cancer. After the entire inconclusive study for the diagnosis of unknown cancer, and while waiting for the histological diagnosis, the patient presented a sudden onset of pallor with neurological alterations with no alterations in head CT, but with MAHA and thrombocytopenia. Given the absence of another clinical entity associated with TMA and a

diagnosis of metastatic carcinoma of unknown origin, the diagnosis of cancer-related MAT was the most probable diagnosis.

Cancer-related TMA is poorly responsive to plasma exchange and immunosuppression (less than 20% response), but this treatment is still recommended. In this entity, the treatment is essentially based on the treatment of the underlying cancer. In this clinical report, treatment with plasma exchange and steroids was started as a life-saving therapy, pending the definitive histological diagnosis. After the histological diagnosis, with no definitive characterization and a progressive clinical and analytical worsening, palliative chemotherapy was initiated, with no response. Cancer-related TMA is associated with a high mortality rate, so it is considered a medical emergency. With no treatment, the mortality associated is greater than 90%. The prognosis for these cases is extremely poor, with most patients passed away within a few weeks after diagnosis (4, 5). In the Lechner et al study nearly half of the 168 patients died within 1 month with or without treatment (4).

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Radiation recall pneumonitis in a patient treated by nivolumab for non-small cell lung cancer, no relapse with rechallenge

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Summary. *Background:* Radiation recall pneumonitis is an inflammatory phenomenon occurring in a previously irradiated area of the lungs in response to precipitating agents. The diagnosis is based on clinical features and radiologic abnormalities in the irradiated field and must occur after the administration of an inciting agent. *Report:* A 58-years-old woman previously treated by left mastectomy and adjuvant radiotherapy for a breast cancer was diagnosed with a right lung adenocarcinoma. Concomitant radio-chemotherapy with irradiation of the upper part of the right hemithorax was performed. Unfortunately, a new metastasis appeared. A new line of treatment with nivolumab was started. Four weeks after the onset of the checkpoint inhibitor, she presented clinical and imaging criteria evoking the diagnosis of RRP induced by nivolumab. A high dose systemic steroid was introduced. As a result, general state, respiratory conditions and imaging features were improved. *Conclusions:* Some drugs are known to be associated with RRP, mainly traditional chemotherapies. Patients generally improved their condition after a break of the precipitating agent and with steroids. RRP induced by nivolumab has only been described once in a Japanese case report. It constitutes the first report of such a case in Europe.

Key words: radiation pneumonitis, immunotherapy, radiation recall reactions

1. Introduction

Nivolumab is an anti-programmed cell death-1 antibody (immunotherapy). Since few years, nivolumab has been approved as second-line treatment of non-small cell lung cancers (NSCLC). The most common side effects, mainly dysimmune toxicities are now well-known (1). Dysimmune toxicities can mainly affect the gastrointestinal tract (colitis, gastritis), the lung (pneumonitis, pleural effusion), the skin (psoriasis, maculopapular rash, DRESS), endocrine system (dysthyroidism, indrenal insufficiency, diabetes), the liver (hepatitis), musculo-articular system (arthritis, myopathies) (1).

Radiation recall reaction (RRR) is an inflammatory phenomenon occurring in a previously irradiated area in response to precipitating agents. Radiation recall pneumonitis (RRP) corresponds to a RRR occurring in a previously irradiated area of the lungs in response to precipitating agents. Main symptoms are fever, dyspnea, dry cough, chest pain and asthenia. The diagnosis is established by radiologic abnormalities (mainly ground-glass opacities) in the irradiated field and triggered after the administration of inciting agents (2). The most commonly involved agents are chemotherapeutic drugs such as taxanes, anthracyclines, gemcitabine (3-5).

This side effect is almost unknown for immunotherapy. We describe here an RRP induced by nivolumab.

2. Case report

In December 2016, a 58-years-old woman was diagnosed with a lung adenocarcinoma in the right upper lobe. She smoked about 10 packs-a-year, and stopped around 25 years ago. Her medical history was marked by a breast cancer treated by left mastectomy and adjuvant radiotherapy in October 2016 (55 Gy). Her non-small cell lung cancer was classified T3N2M1b: the extension work-up revealed mediastinal adenopathies and a single bone metastasis on the anterior superior iliac spine. First-line treatment consisted in neoadjuvant chemotherapy including carboplatin and pemetrexed plus the irradiation of the bone metastasis. In January 2017 she underwent surgery, sadly the primitive lung lesion appeared unresecable. Thereafter concomitant radio-chemotherapy (from February to March 2017 - 66 Gy) including carboplatine and paclitaxel was performed. In April 2017, a new metastasis appeared. Nivolumab was started. Four weeks after the onset of the checkpoint inhibitor, she presented dyspnea, fever, asthenia, cough and mucopurulent expectorations. Chest x-ray showed a right upper lobe interstitial pneumopathy. Thoracic CT scan showed ground-glass opacities and condensations in the field of the thoracic irradiation and in the area of the left breast irradiation (figures 1). Bacterial examination of the sputum sampled before antibiotics was negative. At broncho-alveolar lavage, we found 15% of lymphocytes and 41% of eosinophils, the microbiologic exploration was negative. Nivolumab was stopped for six weeks and high dose systemic steroid was introduced. General and respiratory conditions resolved. The thoracic CT scan performed 6 weeks later showed dramatic improvement (figure 2). The conclusion of the multidisciplinary meeting of our institution was RRP induced by nivolumab especially because of the special distribution of the lesions in fields of previous irradiations (right upper thorax and left breast) what differentiates it from classical immuno-induced pneumopathy. In addition, the multidisciplinary meeting considered that the mechanism of pneumopathy was due to previous irradiations, and that nivolumab was only a trigger, hence the diagnosis of RRP. Nivolumab has been therefore carefully rechallenged without relapse after 22 new cycles.

3. Discussion

Nivolumab is an anti-programmed cell death-1 antibody which is indicated as second-line treatment of non-small cell lung cancer (6, 7). Some drugs are known to be associated with RRP, mainly traditional chemotherapies. RRP has also been described in a patient treated by trastuzumab (8), and in two patients treated with vemurafenib after thoracic radiation of lung metastasis of melanomas (9).

Only one article reporting two cases of RRP induced by nivolumab (10) was found in PubMed. In

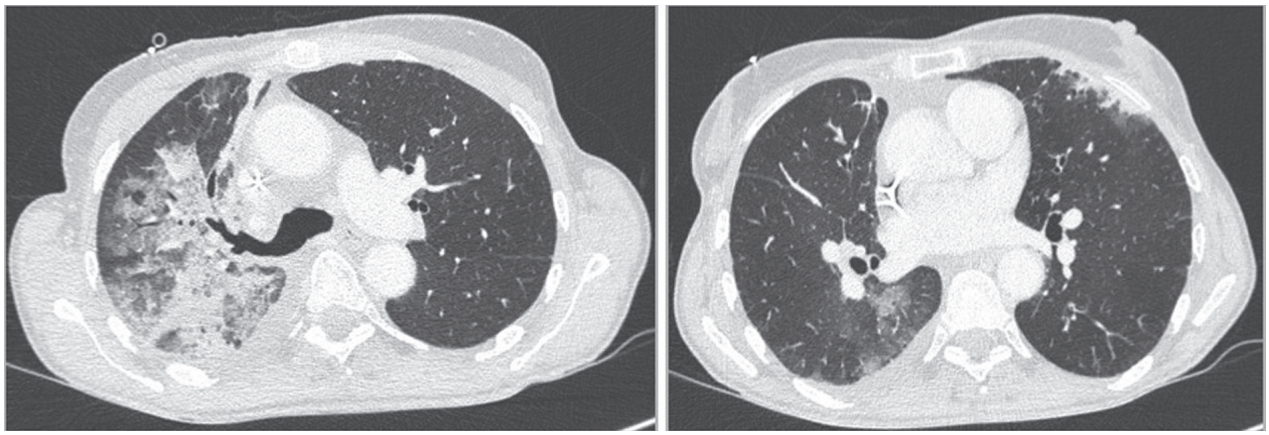

Figure 1. Parenchymal thoracic CT-scan showing condensations and ground-glass opacities in the fields of the thoracic and of the left breast irradiation areas.

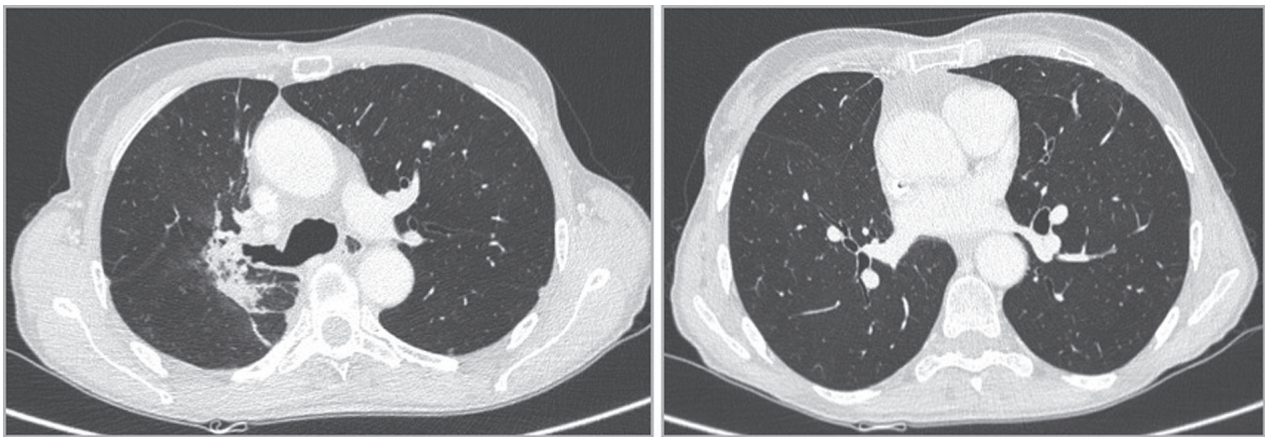

Figure 2. Parenchymal thoracic CT-scan showing improvement in both affected area after systemic steroids therapy.

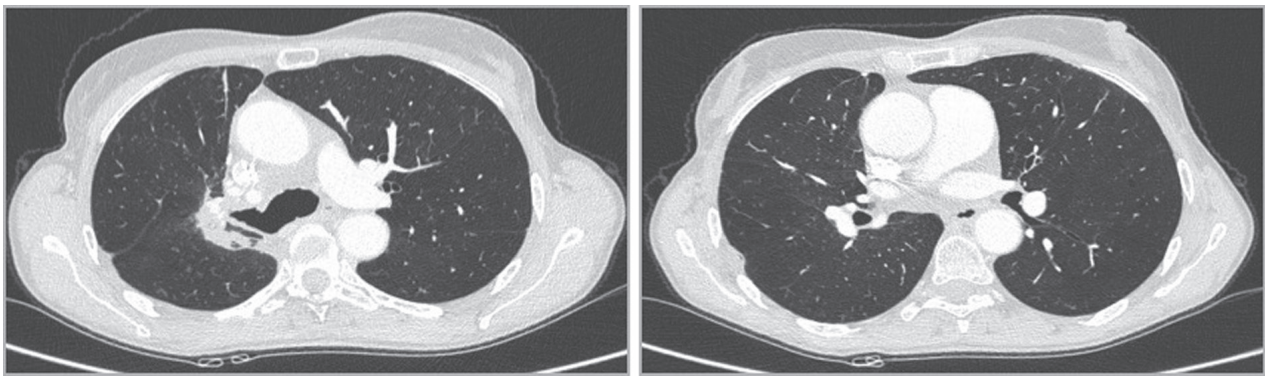

Figure 3. Parenchymal thoracic CT-scan showing no relapse after re-introduction of nivolumab.

general, patients with RRP improved significantly their condition after a break of the nivolumab and with steroids (2, 10).

In our case, the patient presented with two areas of pneumonitis corresponding to the fields of irradiation of the right upper lobe lung cancer and of the left breast cancer while the two radiotherapy sequences were spaced several months apart.

Radiation recall phenomenon is hardly predictable. Some drugs are known to be associated with these reactions but it concerns mainly traditional chemotherapies. Increasing use of immunotherapies such as nivolumab in the treatment of neoplastic diseases explain the emergence of radiation recall reactions due to nivolumab. It mostly concerns dermatitis. RRP induced by nivolumab remains an unknown phenomenon. It must be suspected in patients previously treated by thoracic radiotherapy and developing signs of pneumonitis in the field of radiation while they are treated by nivolumab. The pathophysiology of this phenomenon is unknown but we can assume that its mechanism looks more like that of radiation-induced pneumopathy, because the lesions affect the irradiated parts of the lungs, than that of a pure immuno-induced pneumopathy. So RRP is probably not the same disease than immuno-induced pneumopathy. The treatment consists in systemic corticotherapy and generally allows an improvement or a resolution of the general and respiratory conditions and an improvement of the thoracic CT scan.

The case of our patient was presented to the multidisciplinary staff specifically dedicated to toxicities of immunotherapy at the Gustave Roussy institute. Given a toxicity inferior to a grade 2 CTCAE and the

complete resolution of the toxicity (clinically rather than radiologically), we were allowed to reintroduce the treatment without steroids with a close respiratory monitoring. Nivolumab was resumed the 27th of July 2017. After 22 new cycles of treatment, we did not observe recurrence of RRP (figures 3).

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