Benefit of a Second Opinion

Intrapulmonary Metastases or Multiple Primary Tumors?

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The presence of bilateral pulmonary nodules in lung cancer usually means distant metastases (M1a).[1] We present an extraordinary example that challenged us to look beyond this classification, illustrating the potential benefits of a multidisciplinary re-evaluation in such a case.

CASE REPORT

A 70-year-old male, former smoker, and current marathon runner was diagnosed in September 2005 with a probable squamous cell carcinoma of the right upper lobe (RUL) with (possible) small satellite lesions, a nodule in the right middle lobe (RML), and a nodular structure in the left upper lobe (LUL) on computed tomography (CT) scan, and 18-fluorodeoxyglucose positron emission tomography (FDG-PET) scan. This was considered to be a primary lung cancer with intrapulmonary metastases (stage IV, histology confirmed). The patient received six cycles of chemotherapy doublet (cisplatinum 150 mg on day 1 and gemcitabine 2000 mg on days 1 and 8), which resulted in a slight reduction in size of the lesion in the RUL, and a clear reduction of the lesion in the LUL, although the RML remained unchanged (Fig. 1). Eleven months later, the lesion in the RUL increased in size. A second opinion was arranged.

After reviewing all data and images with repeated PET and CT, the possibility of multiple primary tumors was considered. A video-assisted thoracoscopy, diagnostic wedge excision of the LUL, and a transthoracic biopsy of the RUL were performed, revealing two papillary adenocarcinomas. A wedge excision of the RML, a lobectomy of the RUL, and mediastinal lymph-node dissection showed a 1.8-cm diameter papillary adenocarcinoma of the LUL, a 3.3-cm diameter mixed papillary adenocarcinoma/adenocarcinoma in situ of the RUL, and a 1.1-cm diameter adenocarcinoma in situ of the RML, all radically resected. All nodes were negative. Array-comparative genomic hybridization analysis revealed that all these lesions showed different patterns of gains and losses, consistent with three primary tumors (Fig. 2).[2]

In December 2007, a recurrence in the operation scar of the LUL, and a new abnormality in the left lower lobe (LLL) were observed on CT scan, both 18-FDG-PET positive. Diagnostic wedge excisions of the LUL and LLL and a mediastinal lymph-node dissection were performed. Pathological examination showed two invasive papillary adenocarcinomas (LUL and LLL of 1.5 cm and 0.6 cm diameter, respectively), with free resection margins, without lymph-node metastases. The postoperative course was

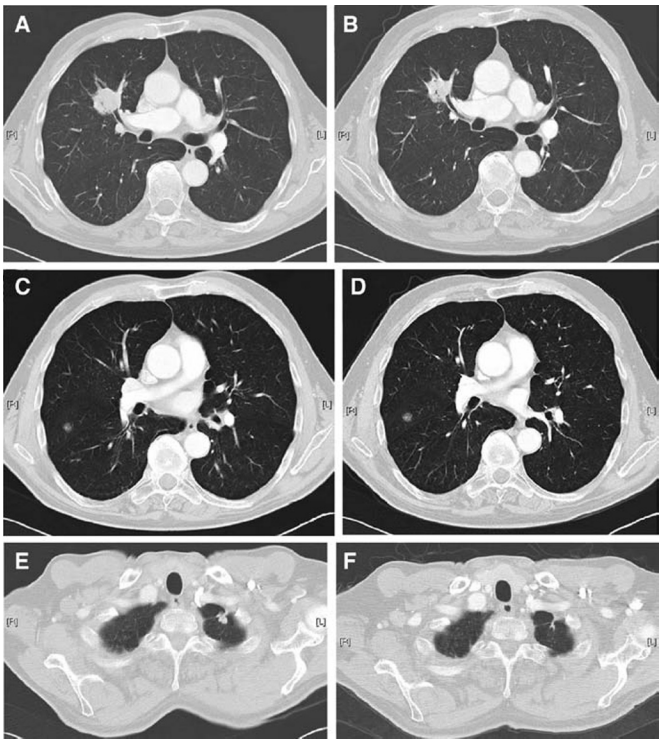

FIGURE 1. Computed tomography scan at time of first presentation and after six cycles of chemotherapy. *A*, Shows a reduction of the lesion in the right upper lobe. *B*, Shows an unchanged right middle lobe lesion. *C*, Shows a clear reduction of the left upper lobe lesion.

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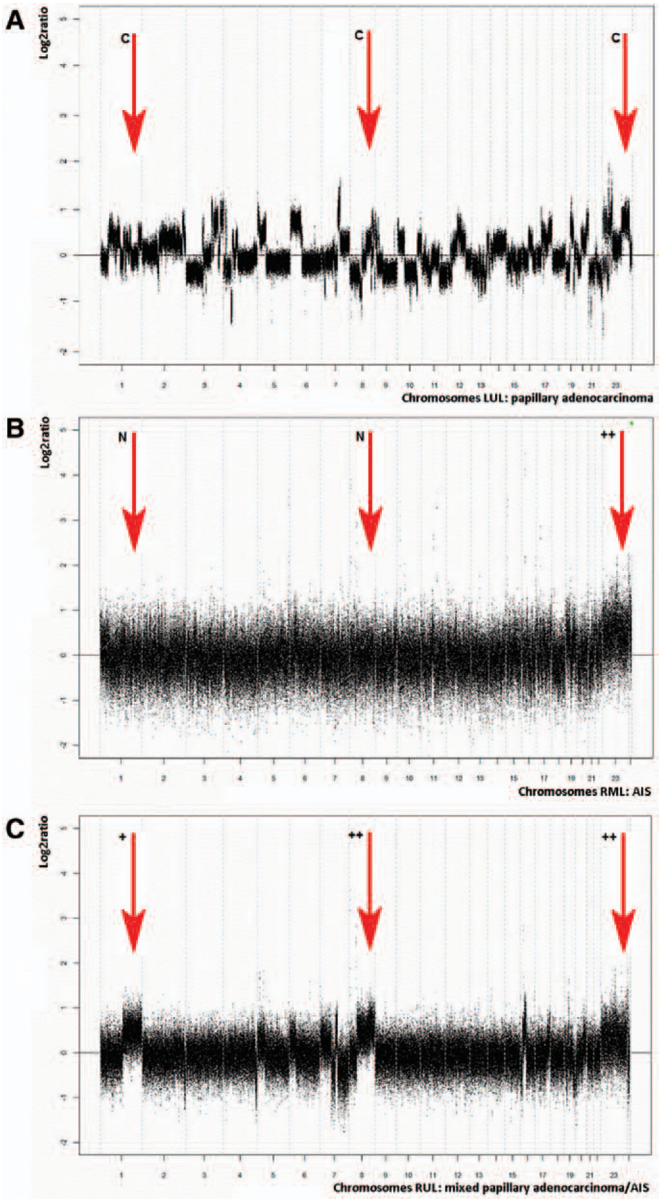

FIGURE 2. Results of array-comparative genomic hybridization analysis. Chromosomal rearrangements as detected by array-comparative genomic hybridization analysis for biopsies of tumor tissue are shown (tumor tissue: epithelium, no selection of invasive or in situ tumor parts). On the *y* axis is the log2 tumor to normal ratio and on the *x* axis the chromosomal position. Gray dots are an average of five-array measurements, because a moving average of five was used for each of the three plots. Gains and losses are positive and negative log2 ratio, respectively. The quality of the three plots are variable, reflecting the use of formalin fixed paraffin embedded clinical material specimens. *A*, Wedge excision apex left upper lobe: papillary adenocarcinoma. *B*, Wedge excision right middle lobe: adenocarcinoma in situ. *C*, Lobectomy material of the right upper lobe: mixed papillary adenocarcinoma/adenocarcinoma in situ. Nontumor DNA of this patient served as reference for each tumor. The arrows and corresponding signs (++,+,N and C) show the most obvious patterns of gains and losses in the chromosomes 1, 8, and X (number 23), with ++ representing a whole chromosomal arm gain, + a partial chromosomal arm gain, N no chromosomal aberrations, and C complex chromosomal band of gains and losses. Plot B is of marginal quality and hence, difficult to interpret. However, as shown by the arrows in the three plots, differences in gains and losses can be observed. The first arrow indicates no chromosomal aberrations in chromosome 1 in plot B versus a complex change in plot A and a partial arm gain in plot C. The second arrow also shows no chromosomal aberration of chromosome 8 in plot B versus a complex change in plot A and a whole chromosomal arm gain in plot C. The third arrow indicates a gain of the entire X chromosome in plot B, much like the X-chromosome gain in the sample of plot C, in contrast with the partial X-chromosome gain in plot A. Gross chromosomal differences are thus detected in the sample of plot B despite the marginal quality, and it is therefore reasonable to conclude that these differences support the assumption of different tumor origins. All array data are available in the Gene Expression Omnibus database, under accession number GSE42377.

uneventful. There have been no signs of recurrence since, and the patient has been alive and well for more than 6 years after the initial diagnosis.

COMMENT

The differentiation between intrapulmonary lung metastases and multiple synchronous primary lung cancers (MSPLCs) may make the prospects for an individual completely different—treatment with either palliative or curative intent. Differentiation between the two requires histopathology and imaging. Separate primary lung tumors can easily be recognized when they are histologically different. In case of identical histological features, genetic analyses such as array-comparative genomic hybridization analysis may be useful in the distinction between MSPLC and metastases.[2] Imaging techniques such as 18-FDG-PET, may be of help by calculating standardized uptake values. Standardized uptake values of the tumors might differ more in patients with second primary tumors than in those with metastatic disease.[3] Furthermore, the growth pattern, lobulized and spiculated aspect on CT may be of help.[4]

An aggressive surgical approach is justified in patients with MSPLC because node-negative disease, and the absence of distant metastases, may result in survival rates comparable with patients with isolated lung cancers.[5] To avoid pulmonary insufficiency limited surgical procedures are preferred. However, the resection must be complete.[2] Patients with MSPLC and node-negative disease should, therefore, be staged separately and if possible, treated as separate entities with curative intent.[6]

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