Virchows Arch (2001) 438:57–65
DOI 10.1007/s004280000313

ORIGINAL ARTICLE

B. Bode-Lesniewska · J. Zhao · E.J.M. Speel
A.M. Biraima · M. Turina · P. Komminoth
P.U. Heitz

Gains of 12q13–14 and overexpression of mdm2 are frequent findings in intimal sarcomas of the pulmonary artery

Received: 10 May 2000 / Accepted: 21 August 2000 / Published online: 30 November 2000

Abstract The characterization of clinical, histopathological, immunohistochemical, and genetic features of intimal sarcomas arising in the pulmonary artery is presented in this study. Four resected lungs, one endarterectomy specimen and three biopsies from eight patients (four males and four females; median age 41 years) suffering from intimal sarcomas of the pulmonary artery using conventional stains, immunohistochemistry, and comparative genomic hybridization (CGH) were analyzed. The predominant clinical presentation was dyspnea (all eight patients) and febrile pulmonary disease (six of eight). Signs of embolic lung disease were present in all patients. One patient died postoperatively, six patients died of disease 8–35 months after presentation, and one patient was alive 6 months after surgery. Histopathological examination of the submitted material showed spindle cell, partially myxoid and pleomorphic sarcomas. Metastases were histologically confirmed in three patients (lung, pleura, and skull). Immunohistochemically, vimentin was strongly expressed in all tumors. Focal positivity was observed for alpha smooth muscle actin, CD117, CD68, p53, and bcl2. No reaction could be obtained for endothelial markers. The proliferation index Ki-67 was between 5% and 80%. Six examined tumors were positive for mdm2. In the CGH analysis, gains and amplifications in the 12q13–14 region were found in six of eight tumors (75%). Other, less consistent alterations, were losses on 3p, 3q, 4q, 9p, 11q, 13q, Xp, and Xq, gains on 7p, 17p, and 17q, and amplifications on 4q, 5p, 6p, and 11q. Intimal sarcomas of the pulmonary artery are tumors with an unfavorable prognosis and poorly differentiated morphology. A majority of tumors show a consistent genetic alteration (gains and amplifications in the 12q13–14 region) and overexpression of mdm2, implicating the mdm2/p53 pathway as a possible mechanism in the tumor pathogenesis.

Keywords Pulmonary artery · Sarcoma · Intimal sarcoma · Immunohistochemistry · Comparative genomic hybridization

B. Bode-Lesniewska (✉) · J. Zhao · P. Komminoth · P.U. Heitz
Department of Pathology, University Hospital,
Schmelzbergstrasse 12, 8091 Zurich, Switzerland
e-mail: beata.bode@kssg.ch
Tel.: +41-1-255-2521, Fax: +41-1-255-4551

A.M. Biraima · M. Turina
Clinic of Cardiovascular Surgery, University Hospital, Zurich, Switzerland

E.J.M. Speel
Department of Molecular Cell Biology and Genetics,
University of Maastricht, Netherlands

Introduction

A large number of neoplasms with various morphology and biology may arise from blood vessels [9]. The phenotype of the tumor cells may resemble endothelium (hemangiomas, hemangioendotheliomas, and angiosarcomas), smooth muscle cells (leiomyomas and leiomyosarcomas), or pericytes (glomus tumors and hemangiopericytomas). A very peculiar and rare tumor with mainly intraluminal growth arising from large arteries is intimal sarcoma [5]. This tumor is considered to develop from subendothelial mesenchymal cells of the vascular wall.

Intimal sarcomas of the great vessels are uncommon. Therefore, mainly case reports and small series of tumors have been published [2, 3, 6, 17, 19]. Since the first intimal sarcoma of pulmonary artery reported by Mandelstamm in 1923 [14], approximately 150 further tumors have been described. Immunohistochemical and electron microscopic examinations suggest a myofibroblastic differentiation of the tumor cells, although an at least partial differentiation along other cell lineages was morphologically documented (chondrosarcomatous, osteosarcomatous, and angiosarcomatous) [8, 11, 12, 17]. The molecular background of these tumors is largely unknown and, to the best of our knowledge, they have not yet been analyzed at the genetic level.

Eight patients suffering from primary pulmonary artery intimal sarcoma were treated between 1994 and

1998 in the Clinic of Cardiovascular Surgery of the University Hospital Zurich, Switzerland. In the present study, we describe: (1) the clinical course and follow-up data, (2) the morphological and immunohistochemical analysis of tumor tissue from these patients, and (3) the results of the comparative genomic hybridization (CGH) analysis of these tumors.

Material and methods

Clinical information was obtained from the files of the University Hospital, Zurich, Switzerland, and follow-up information by contacting the attending physicians. The specimens were fixed in formalin and embedded in paraffin according to standard procedures. Sections (1–2 µm) were cut for conventional histology and immunohistochemistry. Immunohistochemistry was performed on deparaffinized sections using the Ventana NexES automated staining system with diaminobenzidine (DAB) as a substrate. For antigen retrieval, slides were either enzymatically predigested or heated in citrate buffer for 3 min using a pressure cooker. The signal was amplified by catalyzed reporter deposition [1, 4]. Biotinylated tyramine was synthesized according to the method of Bobrow [4]. Slides were counterstained with hemalum. The specifications of antibodies used and working dilutions are summarized in Table 1. The quality of the reactions was controlled on tissue slides with known reaction patterns stained in parallel with the examined probes. Liquid nitrogen snap-frozen tissue was available from the tumors of five patients.

Comparative genomic hybridization

DNA preparation for CGH

Isolation of genomic DNA from frozen tumor samples (five specimens) was performed using the D-5000 Puregene DNA Isolation Kit (Gentra Systems Inc., Minneapolis, Minn., USA). Approximately 2 mm^3 of frozen tumor material was homogenized, and DNA extraction was carried out according to the manufacturer's recommendations. DNA extraction from paraffin-embedded tumors (three specimens) was performed as previously described [27]. Direct fluorescence labeling of DNA was performed by means of nick translation using a commercial kit (BioNick kit, Life Technologies, Gaithersburg, Md., USA).

CGH analysis

CGH was carried out as previously described [27]. The hybridization mixture consisted of 200–400 ng of Spectrum Green-labeled tumor DNA, 200 ng of Spectrum Red-labeled normal reference DNA, and 10 µg of unlabeled human Cot-1 DNA dissolved in 10 µl hybridization buffer [50% formamide, 10% dextran sulfate, and 2× sodium saline citrate (SSC), pH 7.0]. Hybridization took place over 3 days at 37°C to sex-matched normal metaphase spreads (Vysis, Downer Grove, Ill., USA). Digital images were collected from six to seven metaphases using a Photometrics-cooled CCD camera (Microimager 1400, Xillix Technologies, Vancouver, British Columbia, Canada). The software program Quips was used to calculate average green to red ratio profiles for each chromosome. At least four observations per autosome and two observations per sex chromosome were included in each analysis.

Thresholds used for definition of DNA sequence copy number gains and losses were based on the results of CGH analyses of normal tissues. A gain of DNA sequences was assumed at chromosomal regions where the hybridization resulted in a green to red ratio of 1.20. Overrepresentations were considered amplifications when the fluorescence ratio values exceeded 1.5 in a subregion of a chromosome arm. A loss of DNA sequences was assumed at chromosomal regions where the tumor to normal ratio was 0.80. Since some false positive results were found in normal tissues at chromosomes 1p, 16p, 19, and 22, apparent gains at these G–C-rich regions were excluded from all analyses.

Results

Clinical features

The age range of the patients (four males and four females) at presentation was 30–68 years (mean age 48 years; median age 41 years). All patients presented with progressive dyspnea, and six of them had pneumonia or pleuritis. The primary clinical diagnosis was embolic lung disease. One additional patient suffered from superior vena cava compression during the late course of the disease. Five patients were given oral anticoagulant drugs, and six patients received antibiotic therapy for pneumonia and/or pleuritis during their disease. On the

Table 1 Source and dilution of primary antibodies

Antibody	Source	Dilution
Cytokeratin	Biomedicals AG, Augst, Switzerland	1:250
Vimentin	Dako, Glostrup, Denmark	1:500
Desmin	Dako, Glostrup, Denmark	1:20
Alpha-actin	Sigma, St. Louis, Mo., USA	1:20 000
S100	Dako, Glostrup, Denmark	1:500
HMB45	Enzo Diagnostics, Farmingdale, N.Y.	1:50
F VIII	Dako, Glostrup, Denmark	1:1000
CD31	Dako, Glostrup, Denmark	1:10
CD34	Serotec Ldt, Oxford, UK	1:20
CD117	Santa Cruz Biotechnology Inc, Santa Cruz, Calif., USA	1:30
CD99	Novocastra Laboratories, Newcastle upon Tyne, UK	1:25
CD68	Dako, Glostrup, Denmark	1:50
CEA	Bio-Science Products AG, Emmenbruecke, Switzerland	1:10
EMA	Dako, Glostrup, Denmark	1:20
Ki-67	Dianova, Hamburg, Germany	1:30
bcl-1	Novocastra Laboratories, Newcastle upon Tyne, UK	1:10
bcl-2	Dako, Glostrup, Denmark	1:200
p53	Genosys, AMS Biotechnology, Lugano, Switzerland	1:300
mdm2	Dako, Glostrup, Denmark	1:30

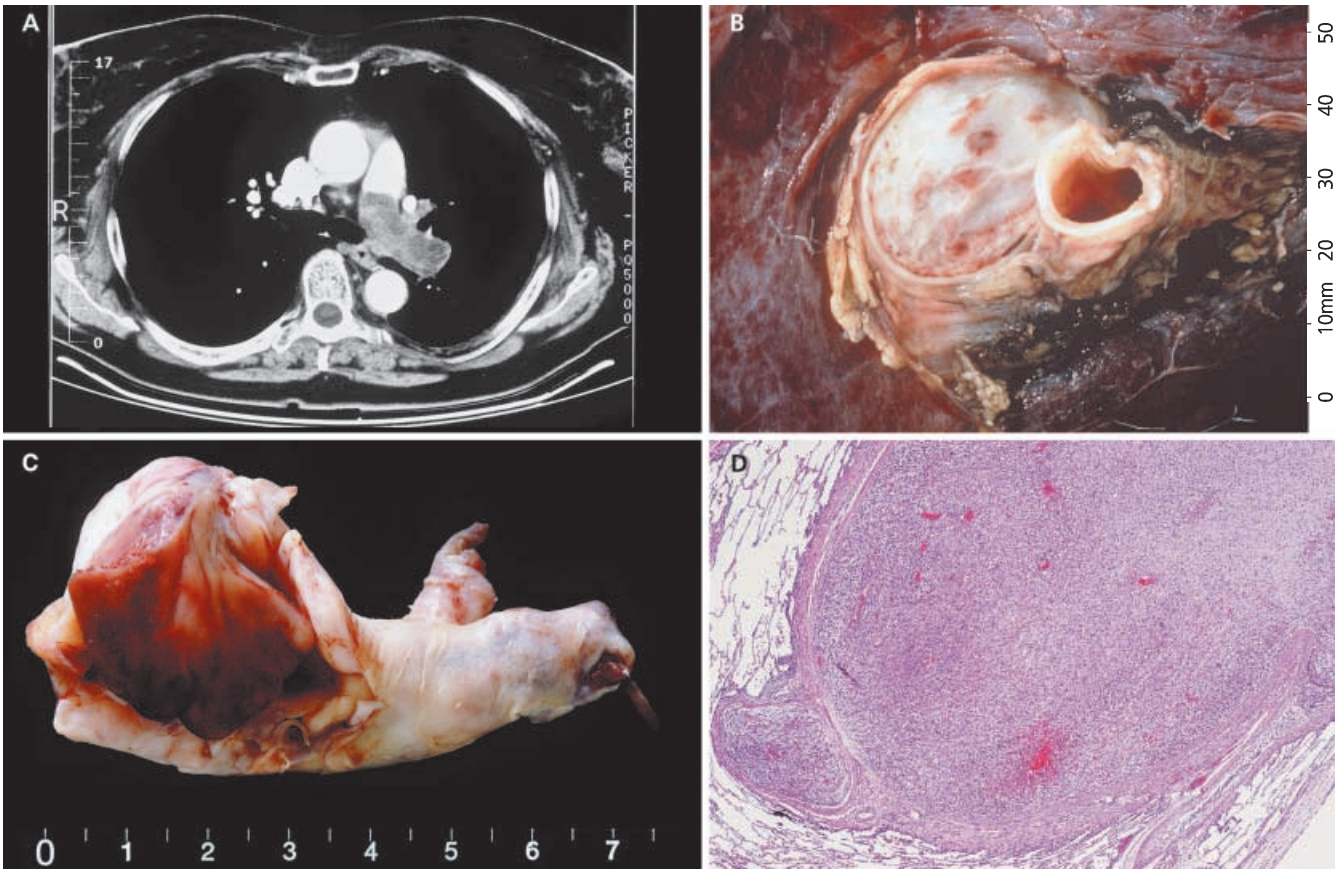

Fig. 1 **A** Computer tomography of the chest of patient 8 with obstruction of the left pulmonary artery by the tumor. **B** View of the hilus of the resected lung of patient 8 with obstruction of the lumen of the pulmonary artery by tumor tissue. **C** Endarterectomy specimen from patient 4. **D** Spreading of the tumor along the intrapulmonary branches of the pulmonary artery; ×25

basis of findings obtained by means of X-ray of the chest, pulmonary scintigraphy, computer tomography (Fig. 1A), magnetic resonance imaging (MRI) combined with MRI-angiography, and heart catheterization combined with pulmonary angiography, a preoperative diagnosis of an intraluminal neoplasia in the pulmonary trunk and/or pulmonary arteries was made in all but one patient (patient 2 in Table 2).

At the time of the clinical work up, three patients (patients 1, 6 and 7 in Table 2) had an inoperable tumor. Four patients underwent a pneumonectomy and resection of the major part of the diseased pulmonary artery. The tumor was removed from the main pulmonary artery to allow the perfusion of the contralateral lung, which was always reduced before surgery. In two patients, the pulmonary artery was reconstructed with xenopericardium. In one patient, resection of the endoluminal tumor mass and the destroyed pulmonary valve was performed. Postoperatively, all but one patient were able to leave the hospital. Six patients died of disease within 8–35 months (mean 20 months) after presentation. Unfortunately, no autopsy could be carried out. One patient was alive 6 months after surgery, receiving adjuvant therapy for residual tumor. One patient died within hours after the pneumonectomy due to the failure of the right heart ventricle. An autopsy of this patient showed no extrathoracic tumor manifestation.

Macroscopy

The pulmonary arteries of all resected lungs (Fig. 1B) were proximally occluded by polypoid intraluminal tumor masses extending distally along the branches of the pulmonary arteries (Fig. 1D). One intrapulmonary and one pleural metastasis was identified. In the four pneumectomy specimens, lung infarctions at various stages of organization were present. The endoluminally resected tumor (Fig. 1C) consisted of a blood vessel luminal casting with gelatinous cut surface.

Conventional histology

The grossly intraluminal growth pattern of the tumors was confirmed by microscopic spreading of malignant cells along the intima (Fig. 2A), sparing the media of the vessel (Fig. 1D). Focal transmural spread with small tu-

Table 2 Data of individual patients. *PT* pulmonary trunk, *LPA* left pulmonary artery, *RPA* right pulmonary artery, *Bx* biopsy, *LPn* left pneumectomy, *RPn* right pneumectomy, *DOD* died of disease, *AWD* alive with disease, *ChTh* Chemotherapy, *RxTh* Radiotherapy

	Age (years)/ Gender	Site of tumor	Surgery	Adjuvant therapy	Metastases/ recurrence	Follow-up
1	41/Female	RPA and mediastinum	Partial lung resection; 5 weeks later palliative bypass between vena cava and right atrium	RxTh 10×3 Gy	Lunge ipsilateral Local recurrence	DOD 30 months after presentation and 15 months after the first surgery
2	41/Male	RPA	Endoluminal tumor resection followed 1 week later with RPn	no	Not known	DOD 9 months after presentation and 4 months after the first surgery
3	68/Male	LPA	LPn	RxTh (30 Gy) of brain metastases	Brain?	DOD 8 months after presentation and 4 months after surgery
4	38/Female	PT and LPA with obstruction of the RPA and destruction of the pulmonary valve	Endoluminal tumor resection and resection of the pulmonary valve	RxTh 54 Gy	Liver? Adrenals? Local recurrence after 24 months	DOD 35 months after presentation and 31 months after surgery
5	30/Female	LPA	LPn	RxTh 64.8 Gy, ChTh	Lung ipsilateral, cervical soft tissue, kidney	DOD 24 months after presentation and 22 months after surgery
6	37/Male	PT, both PAs and left lower lobe artery with infiltration of the mediastinum	Bx of the skull metastasis	ChTh	Skull, lung ipsilateral?	DOD 13 months after presentation and 12 months after biopsy
7	63/Male	PT, LPA, RPA	Bx of the intraluminal mass	ChTh	Not known	AWD 6 months after biopsy
8	67/Female	LPA	LPn, simultanous aorto-coronary bypass (for concurrent coronary heart disease)		Pleura ipsilateral	died postoperatively, 1 month after presentation

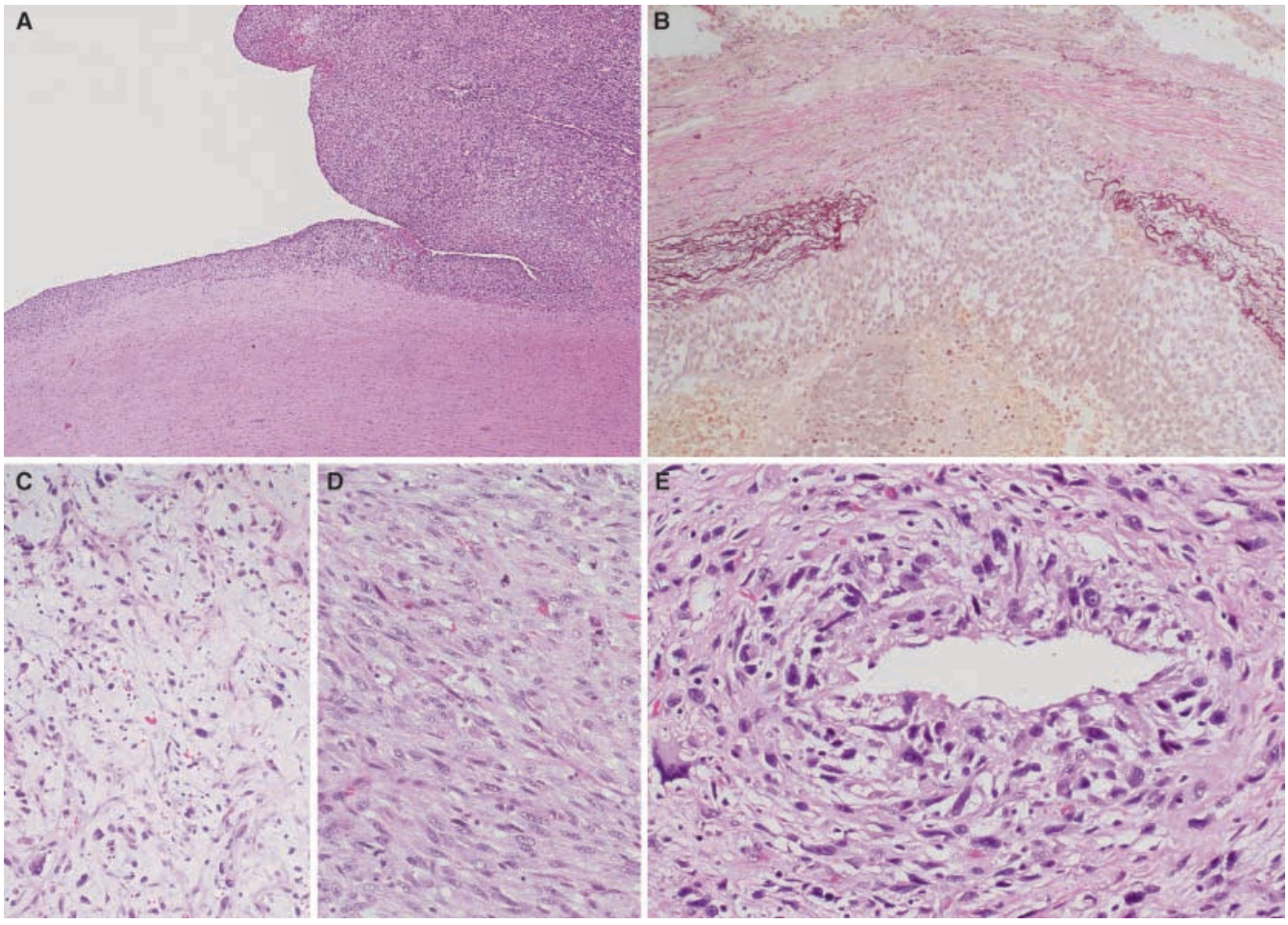

Fig. 2 Histologic details of the tumors. **A** Polypoid tumor mass (*upper right*) spreading along the intima of the wall of the pulmonary artery (*lower half* of the picture). Hematoxylin and eosin (H&E); ×25. **B** Focal destruction of the vessel wall through cellular, partially necrotic tumor mass. Elastin-van Gieson's stain; ×100. **C** Myxoid tumor with low cellular density. H&E; ×100. **D** Bundles of tumor cells resembling leiomyosarcoma. H&E; ×200. **E** An endothelially lined vascular cleft surrounded by pleomorphic tumor cells. H&E; ×200

mor infiltrates in the adventitia and lung parenchyma and foci of necrosis and hemorrhage could be found in four tumors (Fig. 2B). The tissue was composed of a sarcomatous spindle cell proliferation with variable cellular density in all tumors. While five of eight tumors consisted mostly of atypical, small and medium large, spindled or stellate, loosely arranged cells embedded in a myxoid matrix (Fig. 2C), the remaining tumors showed large, highly atypical and pleomorphic cell elements forming solid sheets or cell nests.

Five tumors displayed foci with short fascicles of spindle cells, a pattern resembling leiomyosarcoma (Fig. 2D), whereas in three tumors, the arrangement of cells was haphazardous. Small areas with epithelioid tumor cells were identified in three tumors. Dispersed highly atypical tumor cells were seen in all but one tumor. Four tumors showed a high mitotic rate of up to 25 mitotic figures per 10 HPF and abundant atypical figures. Slits lined by endothelium and surrounded by malignant cells could be observed in primary tumors, representing residual clefts of the original lumen of the affected vessel (Fig. 2E and Fig. 3F). Representative samples of this series of tumors did not display areas of osteosarcoma, chondrosarcoma, angiosarcoma, or rhabdomyosarcoma.

Immunohistochemistry

The results obtained from the immunohistochemical stains are shown in Table 3.Virtually all tumor cells displayed a uniform strong immunohistochemical reaction for vimentin. A focal reaction for alpha smooth muscle actin was seen in all tumors (Fig. 3A). Desmin was focally expressed in two tumors. The reaction for mdm-2 was positive in all six examined tumors, displaying a nuclear signal in the majority of tumor cells in three tumors and in up to 50% of cells in the remaining tumors (Fig. 3B). P53 staining was positive in most cells in one tumor, while it was present only in a small number of cells in six tumors (Fig. 3C).

The proliferation index, as assessed with nuclear staining with Ki-67, showed a range from 5% to 80%

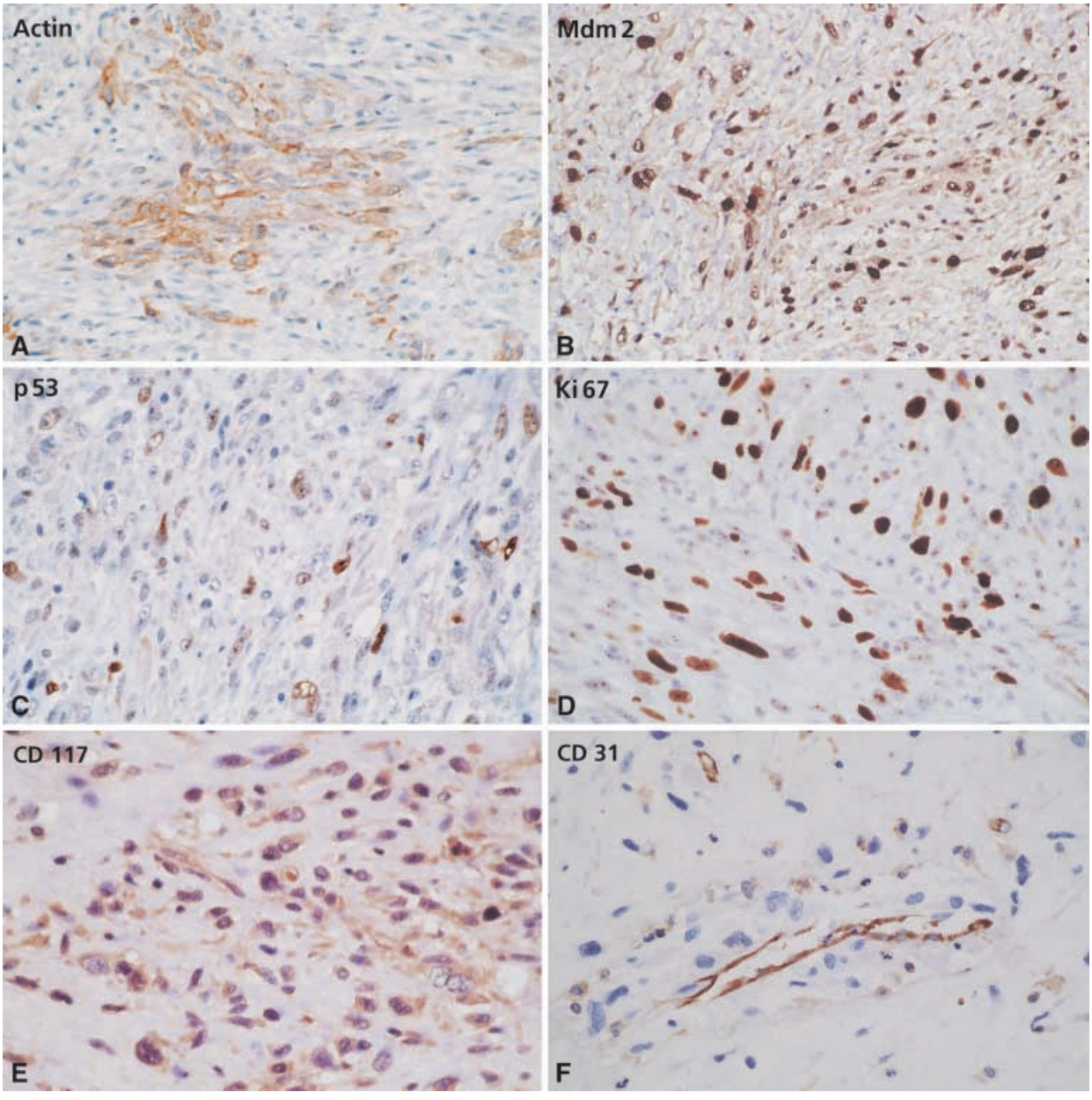

Fig. 3 Immunohistochemical stainings. **A** Alpha-actin: focal tumor cell reaction; ×200. **B** mdm2: nuclear positivity in many tumor cells; ×200. **C** p53: reaction of some tumor cells; ×320. **D** Ki-67: proliferation index of approximately 40%; ×320. **E** CD117: focal reaction; ×320. **F** CD31: reaction of the pre-existing endothelium surrounded by negative tumor cells; ×320

with a mean value of 40% (Fig. 3D). Cytokeratin and EMA were found to be focally expressed in three and two of the tumors, respectively. A weak cytoplasmic reaction was observed for CD117 (Fig. 3E), CD68, and bcl-2 in four, five, and four tumors, respectively. The following immunhistochemical reactions yielded negative results in all examined tumors: CEA, S100, HMB45, FVIII, CD31 (Fig. 3F), CD34, CD99, and bcl-1.

Comparative genomic hybridization

The results of the CGH analysis of eight intimal pulmonary artery sarcomas are shown in Fig. 4. A total of 71 genetic alterations were found in the eight examined tumors, including 34 losses, 26 gains, and 11 amplifications. Individual tumors displayed 1–19 alterations in the amount of genetic material. The most striking changes were found to occur on the long arm of chromosome 12 with the minimal common region 12q13–14, including three amplifications and three gains in six out of eight tumors. Less consistent alterations were losses on the chromosomes 3p, 3q, 4q, 9p, 11q, 13q, Xp and Xq and gains on 7p, 17p and 17q or amplifications on 4q, 5p, 6p and 11q.

Table 3 Results of immunohistochemical stains. *Neg* no reaction obtained; *ND* not done; *(+)* questionable reaction; +1 weak diffuse or focal reaction; +2 moderate reaction; +3 strong diffuse reaction

	1	2	3	4	5	6	7	8
Antibody								
Cytokeratin	Neg	Neg	(+)	Neg	Neg	+1	(+)	Neg
EMA	Neg	Neg	(+)	Neg	Neg	Neg	(+)	Neg
CEA	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg
Vimentin	+3	+3	+3	+3	+3	+3	+3	+3
Desmin	+1	Neg	Neg	Neg	Neg	Neg	Neg	+2
α-smooth muscle actin	+1	+1	+1	+3	+2	+1	+1	+1
S100	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg
HMB45	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg
F VIII	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg
CD31	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg
CD34	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg
CD117	Neg	Neg	+1	+1	+1	Neg	Neg	+1
CD99	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg
CD68	+1	Neg	Neg	+1	+1	+1	+1	+1
Ki-67	5%	70%	80%	20%	30%	50%	40%	50%
p53	+1	+1	+2	Neg	+1	+1	+1	+1
bcl-1	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg
bcl-2	Neg	Neg	Neg	+1	+1	Neg	+3	+1
mdm2	+3	+3	ND	+2	+1	+2	ND	+3

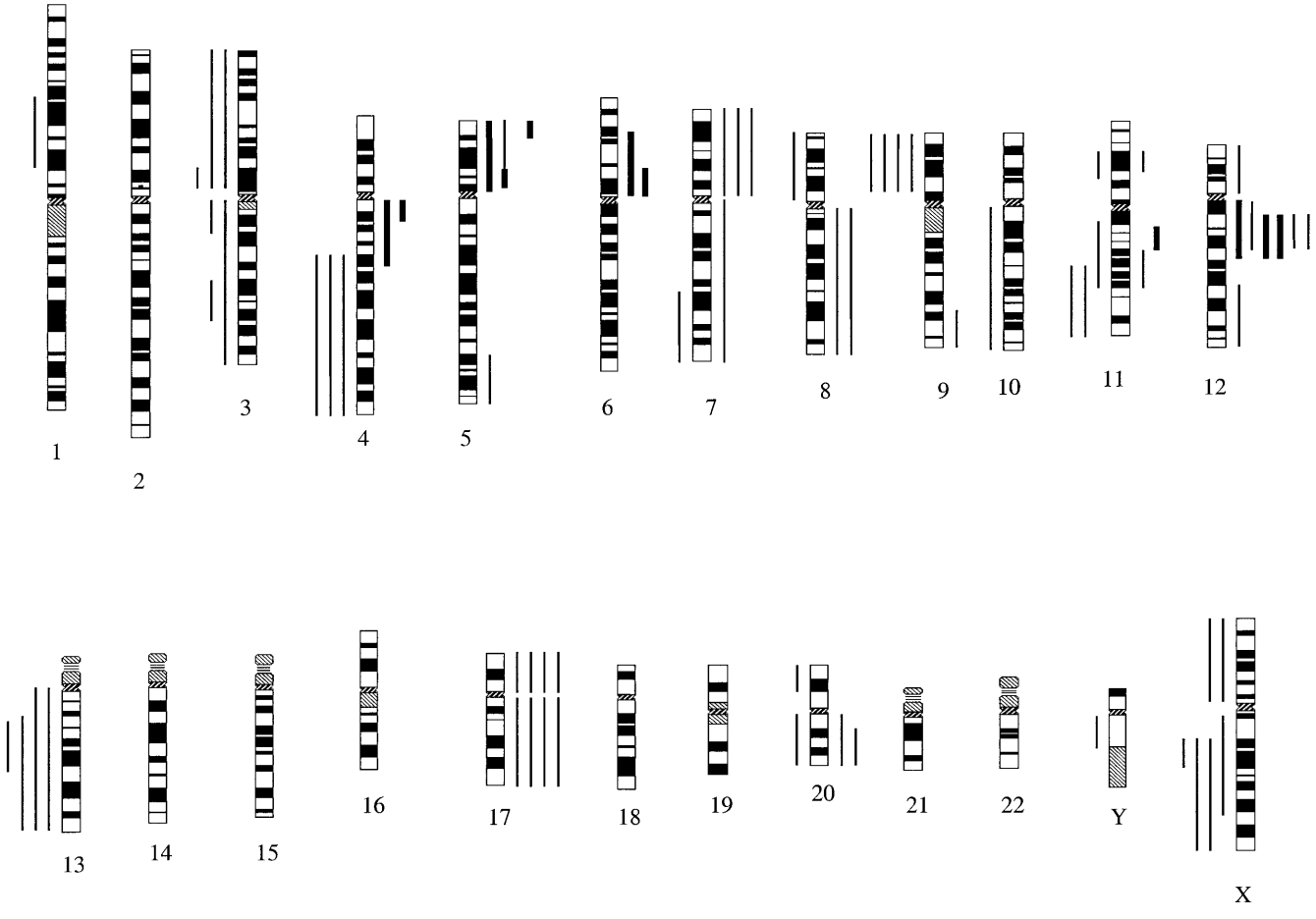

Fig. 4 Results of the comparative genomic hybridization (CGH) analysis of eight intimal pulmonary artery sarcomas. Bars to the *left* of the chromosomes correspond to losses, bars to the *right* correspond to gains, and *thick* bars correspond to amplifications of the genetic material

Discussion

Primary malignant intravascular tumors of the pulmonary artery are uncommon. Recent progress in the diagnostic procedures, enabling differentiation between vascularized tumor tissue and intraluminal thrombus [2, 20], has made an intra vitam diagnosis possible. Prior to the introduction of these powerful techniques, a diagnosis was made mainly at postmortem examination [3, 26]. However, sarcomas of the pulmonary arteries were, and still are, tumors with a poor clinical outcome irrespective of the treatment. In fact, survival in general is a little more than 1 year after the initial presentation [2, 23], a survival of up to 5 years being an exception [6]. In the present series, six patients died of tumor within 8–35 months (mean 20 months) after the appearance of first symptoms despite adjuvant therapy and extensive surgical resection. An early diagnosis, unfortunately, has not markedly prolonged survival. The aggressiveness of the tumor was confirmed in this series by an often advanced extent of the tumor at the diagnosis and a high overall metastatic rate.

The role of the pathologist in the management of patients suffering from intimal sarcomas of the pulmonary artery is to recognize the intraluminal mass as a sarcoma and to differentiate it from an organizing thrombus, a metastasis of a malignant melanoma, or a carcinoma using routine and immunohistochemical methods. Since there are no unequivocal histopathological or immunohistochemical markers of intimal sarcoma, pulmonary artery as the site of the primary tumor has to be confirmed through comprehensive clinical staging.

Histologically, most primary tumors of the pulmonary artery are sarcomas spreading as intraluminal masses along the intimal surface of the vessel in a sheet-like manner (intimal sarcomas). Non-intimal, mural sarcomas of the pulmonary artery are exceedingly rare and are difficult to differentiate from primary sarcomas of the lung. In the literature, the majority of intimal sarcomas are described as poorly differentiated, often myxoid and pleomorphic sarcomas, often with immunohistochemical and ultrastructural signs of myofibroblastic differentiation [5, 12, 17]. The second most common category is a leiomyosarcoma. The two tumor types (including tumors classified as malignant fibrous histiocytoma and myxofibrosarcomas) comprise up to 80% of the reported tumors. The remaining tumors contained areas of osteosarcoma, chondrosarcoma, angiosarcoma, or rhabdomyosarcoma or, very rarely, liposarcoma [5, 6, 12, 17, 19]. No such elements were observed in representatively sampled tumors in our series.

In accordance with the results of previous studies [5, 6, 12], the immunohistochemical expression of vimentin was very strong in contrast to less pronounced expression of alpha smooth muscle actin. Weak focal expression of desmin and epithelial markers were found in two and three tumors, respectively. Although these findings are not specific, they are compatible with the hypothesis of a myofibroblastic differentiation of at least part of the tumor cells, as generally indicated in the literature [6, 12, 17]. No expression of endothelial markers (factor VIII, CD31, CD34) could be found. Interestingly, a weak focal reaction was demonstrated in half of the tumors using the antibody against c-kit (CD117), a marker of hematopoietic progenitor cells, mast cells, melanocytes, germ cells, and Cajal cells of the gastrointestinal tract. The positive reaction for CD117 is highly sensitive for gastrointestinal stromal tumors, but focal reactivity has been reported in other mesenchymal lesions of various origin, such as dermatofibrosarcoma protuberans, clear cell sarcoma, or, rarely, malignant fibrous histiocytoma [21]. In the recently published study [15], a positive reaction for CD 117 was found in over a half of the examined angiosarcomas and in some cases of Kaposi sarcomas. Intimal sarcoma seems to be another vascular (but not endothelial) tumor with occasional CD 117 expression. Bcl-2 oncoprotein expression was found in four tumors, which confirms variable expression of this epitope in soft tissue sarcomas described by Suster [22].

Amplifications and gains on the long arm of chromosome 12 with the minimal common region 12q13–14 in 75% of tumors were the most striking findings of the CGH examination of the current series of intimal pulmonary artery sarcomas. It is particularly interesting that this entity, showing pronounced morphologic heterogeny at the microscopic level, seems to present with a consistent genetic alteration. 12q12–21 was one of the very first amplifications demonstrated using CGH [13]. Multiple genes are coamplified as a part of the 12q13–15 amplification unit: mdm2, sas, cdk4, and hmgi-c genes being the most consistently amplified and overexpressed in different types of sarcomas. Atypical lipomatous tumors contain in over 90% of cases amplified genetic material of this region in the form of supranumerary ring chromosomes [13].

The mdm2 gene has been shown to be up-regulated in many human neoplasias with the highest frequency of gene amplification in soft tissue tumors (20%), osteosarcomas (16%), and esophageal carcinomas (13%) [16]. In our series, overexpression of mdm2 could be confirmed by means of immunohistochemistry in all examined tissue samples, including two tumors with no increase in genetic material on 12q in the CGH analysis. The mdm-2 protooncogene is a negative regulator of p53 activity [16, 25, 28], acting through binding of the p53 protein and accelerating its degradation. Although frequently mutated in soft tissue sarcomas, the p53 gene was often found in its wild form in sarcomas overexpressing mdm2 [16, 18]. The presence of the p53 protein in intimal sarcomas of the pulmonary artery could be shown by means of immunohistochemistry in seven of eight tumors examined in our series. However, mutation analysis has not been performed.

Wunder [25] noted frequent involvement of 12q13–15 in low-grade paraosteal osteosarcomas in contrast to aggressive intramedullary tumors and in soft tissue sarcomas with generally low-grade or borderline malignant potential and suggested a possible predisposing role of this region for slow growing, low-grade tumors which commonly present as a large mass without metastasis. The results of the present study of intimal sarcomas, which are prognostically unfavorable, often high-grade tumors, do not support this hypothesis.

Other genetic changes in intimal sarcomas found in our study have been previously reported in other malignancies [13]: amplification of the centromeric region of 4q in a small number of sarcomas; losses on 4q in carcinomas; amplifications on 5p in carcinomas, osteosarcomas, and malignant fibrous histiocytomas; amplifications on the 6p in several types of malignancies, such as lymphomas, sarcomas, melanomas, or some carcinomas; gains and amplifications of 8q in various kinds of tumors; gains and amplifications of 17p in some cases of osteosarcoma and leiomyosarcoma; and amplification of 17q mostly in some carcinomas but also in malignant peripheral nerve sheath tumors. The frequent deletions of chromosome 13 (four of eight of the tumors in the present series) suggest that loss of the retinoblastoma tumor suppressor gene may be involved in tumorigenesis. Other chromosomal regions which are frequently altered in soft tissue sarcomas, such as 1p, do not seem to be involved in intimal sarcomas of the pulmonary artery.

Of the tumor types remotely histologically related to intimal sarcomas of the pulmonary artery, leiomyosarcomas show frequent karyotypic changes on chromosome 12q [10], but no changes in the amount of genetic material (despite complicated alterations) in this region were found in the CGH analysis [7, 13]. In addition, no karyotypic changes of chromosome 12 were observed in three myofibroblastic sarcomas [10].

In conclusion, intimal sarcomas of the pulmonary artery remain tumors with poor prognosis. Although etiology and pathogenesis of this rare tumor remain to be elucidated, our results of frequent amplifications and gains in the 12q13–14 region combined with overexpression of mdm2 suggest a role of the mdm2/p53 pathway in the tumorigenesis of intimal sarcomas. In the future, these findings may serve as a basis for therapeutic intervention as soon as substances modifying the mdm2-p53 interaction are available [24].

Acknowledgments We thank Prof. R. Maurer, City Hospital Triemli, Zürich, Switzerland for supplying the tumor tissue of patient 7. We are grateful to our photographers I. Schmieder and N. Wey for their assistance.

References

1. Adams JC (1992) Biotin amplification of biotin and horseradish peroxidase signals in histochemical stains. J Histochem Cytochem 40:1457–1463
2. Anderson MB, Kriett JM, Kapelanski DP, Tarazi R, Jamieson SW (1995) Primary pulmonary artery sarcoma: a report of six cases. Ann Thorac Surg 59:1487–1490
3. Babatasi G, Massetti M, Galateau F, Khayat A (1998) Pulmonary artery trunk leiomyosarcoma. Thorac Cardiovasc Surg 46:45–47
4. Bobrow MN, Harris TD, Shaughnessy KJ, Litt GJ (1989) Catalyzed reporter deposition, a novel method of signal amplification. J Immunol Methods 125:279–285
5. Burke A, Virami R (1993) Tumors of the great vessels. A clinicopathologic study. Cancer 71:1761–1773
6. Burke A, Virami R (1996) Tumors of the great vessels. In: Burke A, Virami R (eds) AFIP atlas of tumor pathology. Tumors of the heart and great vessels. AFIP Washington DC, pp 211–227
7. El-Rifai W, Sarlomo-Rikala M, Knuutila S, Miettinen M (1998) DNA copy number changes in development and progression in leiomyosarcomas of soft tissues. Am J Pathol 153:985–990
8. Emmert-Buck MR, Stay EJ, Tsokos M, Travis WD (1994) Pleomorphic rhabdomyosarcoma arising in association with the right pulmonary artery. Arch Pathol Lab Med 118:1220–1222
9. Enzinger FM, Weiss SW. Soft tissue tumors, 3rd edn., Mosby, St. Louis, p 1995
10. Fletcher CD, Dal Cin P, de Wever I et al. (1999) Correlation between clinicopathological features and karyotype in spindle cell sarcomas. A report of 130 cases from the CHAMP study group. Am J Pathol 154:1841–1847
11. Goldblum JR, Rice TW (1995) Epithelioid angiosarcoma of the pulmonary artery. Hum Pathol 26:1275–1277
12. Johansson L, Carlen B (1994) Sarcoma of the pulmonary artery: report of four cases with electron microscopic and immunohistochemical examinations, and review of the literature. Virchows Arch 424:217–224
13. Knuutila S, Bjorkqvist AM, Autio K, et al. (1998) DNA copy number amplifications in human neoplasms: review of comparative genomic hybridization studies. Am J Pathol 152:1107–1123
14. Mandelstamm M (1923) Über primäre Neubildungen des Herzens. Virchows Arch 245:43–47
15. Miettinen M, Sarlomo-Rikala M, Lasota J (2000) KIT expression in angiosarcomas and fetal endothelial cells: lack of mutations of exon 11 and exon 17 of c-kit. Mod Pathol 13:536–541
16. Momand J, Jung D, Wilczynski S, Niland J (1998) The mdm2 gene amplification database. Nucleic Acids Res 26:3453–3459
17. Nonomura A, Kurumaya H, Kono J et al (1988) Primary pulmonary artery sarcoma. Report of two autopsy cases studied by immunohistochemistry and electron microscopy, and review of 110 cases reported in the literature. Acta Pathol Jpn 38:883–896
18. Oliner JD, Kinzler KW, Meltzer PS, George DL, Vogelstein B (1992) Amplification of a gene encoding a p53-associated protein in human sarcomas. Nature 358:80–83
19. Parish JM, Rosenow EC, Swensen SJ, Crotty TB (1996) Pulmonary artery sarcoma. Clinical features. Chest 110:1480–1488
20. Rafal RB, Nichols JN, Markisz JA (1995) Pulmonary artery sarcoma: diagnosis and postoperative follow-up with gadolinium-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imagining. Mayo Clin Proc 70:173–176
21. Sarlomo-Rikala M, Kovatich MS, Brusevicius A, Mitettenen M (1998) CD117: a sensitive marker for gastrointestinal stromal tumors that is more specific than CD34. Mod Pathol 11:728–734
22. Suster S, Fisher C, Moran CA (1998) Expression of bcl-2 oncoprotein in benign and malignant spindle cell tumors of soft tissue, skin, serosal surfaces, and gastrointestinal tract. Am J Surg Pathol 22:863–872
23. Thiele A (1996) "Wandering pneumonia" in primary pulmonary artery sarcomas. Pathologe 17:231–234
24. Wang H, Zeng X, Oliver P, et al. (1999) MDM2 oncogene as a target for cancer therapy: an antisense approach. Int J Oncol 15:653–660
25. Wunder JS, Eppert K, Burrow SR, Gogkoz N, Bell RS, Andrulis IL (1999) Co-amplification and overexpression of CDK4, SAS and MDM2 occurs frequently in human parosteal osteosarcomas. Oncogene 18:783–788
26. Zerkowski HR, Hofmann HS, Gybels I, Knolle J (1996) Primary sarcoma of pulmonary artery and valve: multimodality treatment by chemotherapy and homograft replacement. J Thorac Cardiovasc Surg 112:1122–1123
27. Zhao J, Speel EJM, Muletta-Feurer S, et al. (1999) Analysis of genomic alterations in sporadic adrenocortical lesions. Am J Pathol 155:1039–1045
28. Zietz C, Rossle M, Haas C, Sendelhofert A, Hirschmann A, Sturzl M, Lohrs U (1998) MDM-2 oncoprotein overexpression, p53 gene mutation, and VEGF up-regulation in angiosarcomas. Am J Pathol 153:1425–1433