Number 12 Winter 2012

European Society of Pathology

Pathology newsletter

Table of Contents:

Word from the President Prof. F. Carneiro

In this winter issue of the Newsletter, I will briefly summarize the initiatives recently undertaken by our Society.

The 24th ECP was held in Prague (8-12 September 2012), twenty-five years after the 11th ECP, held also in Prague, in September 1987. It was a very successful meeting, attended by 2,434 participants, from 85 countries, encompassing 1,955 registered delegates, 166 accompanying persons and 313 exhibitors/sponsors. The success was due to the superb performance of Prof. Ales Ryska (Chairman of the Local Organizing Committee) and his collaborators. Only those who have been involved in the organization of a big Congress may understand what was done in such a quiet, confident and professional way. The scientific sessions were generally very good and the programme was well balanced, covering the most important areas of "modern" Pathology. The social events gathered participants in a friendly and relaxed atmosphere and the excellent quality of food and wine helped a lot. The D. Giovanni opera in the Estates Theatre deserves a special mention. It was really a delightful and rather unique occasion. Prague, as one of the most beautiful cities in Europe, attracted people to touristic crawls and the weather contributed also for the extremely nice atmosphere.

The upcoming 25th ECP will be held in Lisbon (31 August to 4 September, 2013). The *motto* of the Congress is "Pathology: A gate to the future", having in mind the new challenges of Pathology and the future Pathologists — Residents and Trainees have been stimulated and are playing already a crucial role in the organization of several sessions. The Lisbon Congress was initially coined the seven Ps Congress: **P**athology after **P**rague; **P**rognosis; **P**redictive; **P**ersonalized; **P**ortugal and **P**leasure. The finalized social program has expanded this number of Ps: a couple of exciting **P**arties, including a Sunset Rave Party (Residents' *fiesta*), a Performance of choral music pieces from Portuguese speaking countries and a Opening Ceremony devoted to FADO (it is a pity it is not written Phado). Tunas of the Faculty of Medicine of Porto University will bring a touch of joy to the Closing Ceremony and Congress Party.

The scientific programme for Lisbon Congress is almost finished. The core of the programme is being prepared with a strong input from all ESP Working Groups. The programme will include also contributions from the Portuguese Society of Pathology, the ESP Associated Societies and other leading International Organizations such as EORTC, OECI, UEG, ESMO and Arthur Purdy Stout Society. A wide range of scientific sessions will be offered, comprising Slide Seminars, Short Courses, Symposia, Videomicroscopy and Special Sessions, as well as Oral Free Paper and Poster Sessions. Four Keynote Lectures will address some hot topics of the present and the future of Pathology. Attendance of all sessions, including Slide Seminars, will be free. Speakers will be offered a 50%

Continues on p.2

European Society of Pathology

Pathology newsletter

Continues from p.1

reduced registration. Bursaries will be attributed to Residents and Trainees. The organizers hope that the scientific programme and social activities will constitute a strong stimulus for your participation in the Congress. It will be a pleasure to welcome all ESP members in the capital of Portugal and thus contribute to consolidate the Congresses of the ESP as the most important meetings of Pathologists in Europe.

Further, the ESP is preparing the 26th ECP to be held in London, from 30 August to 3 September, 2014. This Congress will be jointly organized by the ESP and the Pathological Society of Great Britain & Ireland. Officers of both Societies participated recently in a planning meeting in Brussels and have agreed on the most important financial and organizational issues.

Future Congresses approved by the General Assembly of the ESP will be held in Belgrade (2015) and Cologne (2016), the latter jointly organized by the ESP and the German Division of the IAP. Venues for future ECPs (2017 and after) are being evaluated by CPO Hanser, the Professional Congress Organizer responsible for the technical organization of the ESP Congresses.

The Education Committee is developing all efforts to create a dynamic and attractive Education Portal that we hope will be opened to the ESP members along 2013.

In the frame of the activities of the European Association of Pathology Chairs and Program Directors (EAPCP), a specialty test on gastrointestinal pathology was recently organized, and a proficiency progress test will be launched very soon. In the specialty test, 261 participants from 60 countries completed the test. Feedback from participants was very positive, including suggestions for future tests and the request that these tests continue to be offered.

The ESP goes on fostering the cooperation with other International Organizations and Societies: 1) The ESP is involved in a direct collaboration with the EORTC and the Sanger Institute, addressing next generation sequencing issues on FFPE tissues; 2) Fred Bosman organized the ESP/ESMO Joint Symposium on “Molecular Diagnostics for Personalized Cancer Treatment”, for the ESMO Congress held in Vienna, in September/October 2012; 3) The collaboration with UEG has also been very fruitful and a joint ESP/UEG multidisciplinary session on “Endoscopy meets pathology: Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD)” was organized at UEG Week, attracting more than 1,000 participants; 4) The collaboration with the UEMS is being reinforced and the upcoming meeting will be held at the ESP headquarters on 15 December, 2012; 5) The collaboration with the International Academy of Pathology (IAP) is also being reinforced and the ESP officers organized an “European Society of Pathology Symposium” in the IAP Congress held in October, 2012, in Cape Town.

The quality assurance programme in molecular pathology is moving ahead successfully under the coordination of Han van Krieken.

A task force was developed for the revision of the ESP Statutes and Bylaws in order to acknowledge recent and future developments of the Society.

I take this opportunity as President to thank you all for your continuing support of the European Society of Pathology and to wish you a Merry Christmas and a prosperous New Year.

Fátima Carneiro

European Society of Pathology

Pathology newsletter

In illo tempore

Portuguese pathology and the European Society of Pathology

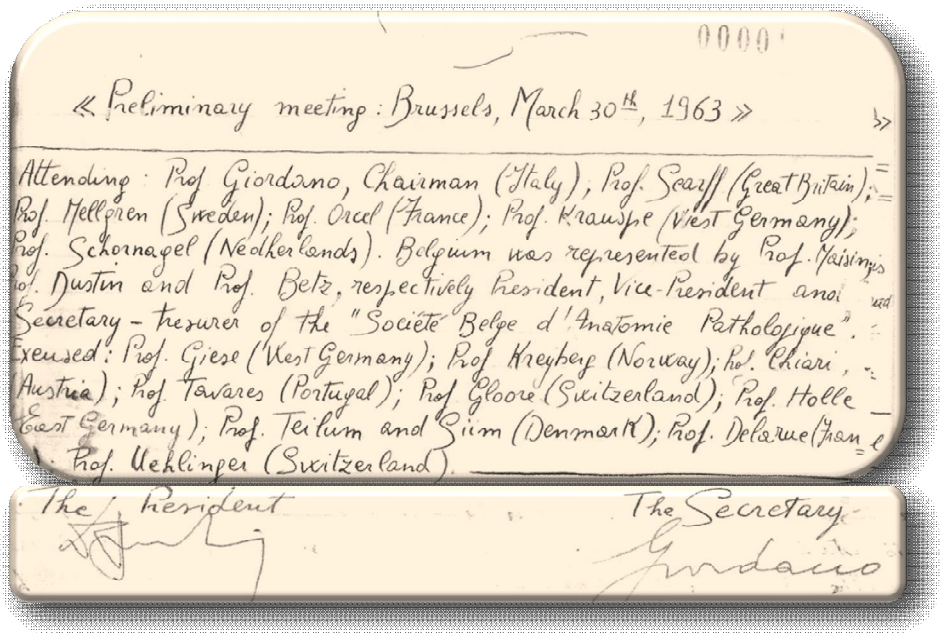
Prof. Amândio Tavares, Director of the Pathology Institute and Rector of Porto University, could not attend the Foundation Meeting of the European Society of Pathology that was held in Brussels in March 30, 1963. In the respective minutes, Prof. Tavares appears, like other major personalities of European Pathology, such as Prof. Kreyberg and Prof. Teilum, under the term "Excused" (Fig.1).
The links of Portuguese pathologists with the ESP restarted in 1971 during the Castrocaro Terme Congress of the ESP and were reinforced in the late seventies and early eighties *via* the Council of the National Representatives.
Prof. Daniel Serrão, who had succeeded to Prof. Tavares in Porto, made a proposal to organize a future Congress of the ESP (1987 or 1989) during the Helsinki Congress (September, 1981). At the Executive Committee meeting held in Hamburg on September 19, 1983, under the Presidency of Prof. Ferluga, Prof. Serrão gave the Committee more precise details about the 1989 Congress, to be organized in Porto, Portugal (Fig.2). Curiously, in the minutes of the Meeting it is written that the Congress would take place in Lisbon (Profs. Giordano and Ferluga were 24 years ahead…).

The formal acceptance of Porto as the site for the 12th Congress was made in the General Assembly of the ESP during its 10th Congress in Athens (President: Prof. Johannessen; Secretary: Prof. Falkmer). Jan V. Johannessen informed about the forthcoming European Congresses of Pathology: Prague (1987), Porto (1989) and Ljubljana (1991) (Fig.3).

Although we realize we are biased, we think that the 1989 Porto ECP was a big success, having gathered more than 1,300 delegates from the five continents of the world. The same holds true for the first Intercontinental Congress of Pathology, held in Funchal, Madeira Island, in 2000 (Fig.4). We are convinced it will be also true for the next Congress to be held in Lisbon from August 31 to September 4, 2013.

Porto, December 10, 2012
Fátima Carneiro Manuel Sobrinho Simões

Fig. 1 - Minutes of the foundation meeting of the European Society of Pathology Brussels, March 1963


0000

« Preliminary meeting : Brussels, March 30th, 1963 »

Attending : Prof. Giordano, Chairman (Italy), Prof. Scarff (Great Britain); Prof. Hellgren (Sweden); Prof. Oberl (France); Prof. Krauspe (West Germany); Prof. Schornagel (Nedkerlands). Belgium was represented by Prof. Naisimis Prof. Dustin and Prof. Betz, respectively President, Vice-President and Secretary - tresurer of the "Societe Belge d'Anatomie Pathologique". Excused: Prof. Giese (West Germany); Prof. Kreyberg (Norway); Prof. Chiari, (Austria); Prof. Tavares (Portugal); Prof. Gloore (Switzerland); Prof. Holle (East Germany); Prof. Teilum and Siim (Denmark); Prof. Delarue (Jean ? Prof. Uehlinger (Switzerland).

The President

The Secretary

Giordano

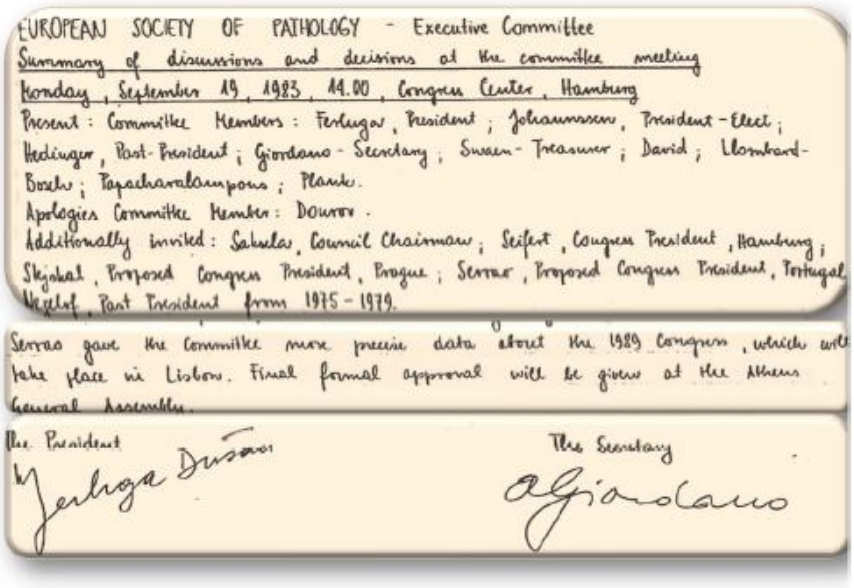
Continues on p. 4

European Society of Pathology

Pathology newsletter

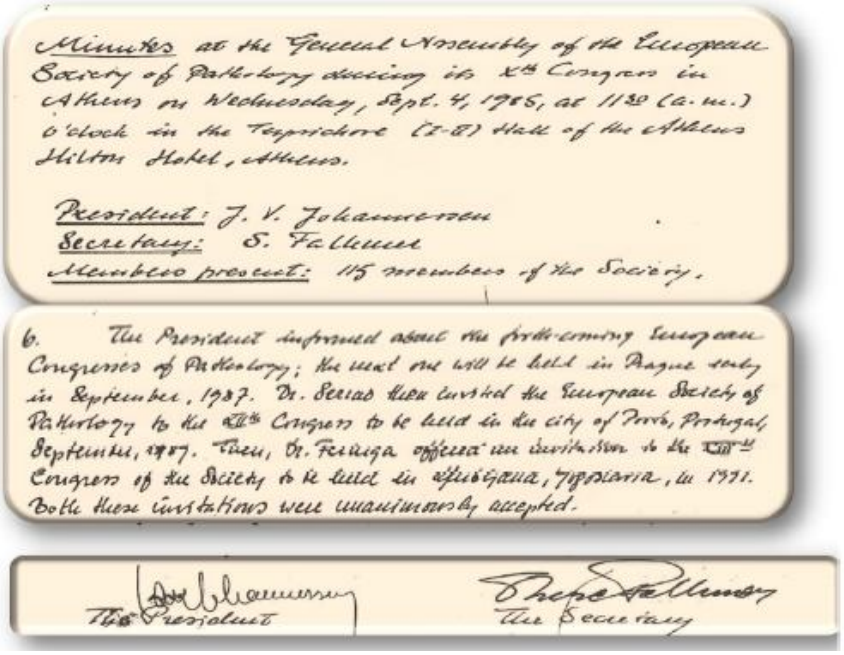
Continues from p. 3

Fig. 2 - Minutes of the ESP Executive Committee meeting
Hamburg, September 1983



EUROPEAN SOCIETY OF PATHOLOGY - Executive Committee
Summary of discussions and decisions at the committee meeting
Monday, September 19, 1983, 14.00, Congress Center, Hamburg
Present: Committee Members: Feriuga, President; Johannessen, President-Elect; Hedinger, Past-President; Giordano-Secretary; Swaen-Treasurer; David; Lombard-Bouche; Papacharalampous; Plante.
Apologies Committee Member: Doutre.
Additionally invited: Sabiston, Council Chairman; Seifert, Congress President, Hamburg; Skjoldal, Proposed Congress President, Prague; Serras, Proposed Congress President, Portugal; Wegelius, Past President from 1975-1979.
Serras gave the Committee more precise data about the 1989 Congress, which will take place in Lisbon. Final formal approval will be given at the Athens General Assembly.
The President — The Secretary

Fig. 3 - Minutes of the General Assembly of the ESP
Athens, September 1985



Minutes of the General Assembly of the European Society of Pathology meeting in XIth Congress in Athens on Wednesday, Sept. 4, 1985, at 11.30 (a.m.) o'clock in the Tsypriohore (I-8) Hall of the Athens Hilton Hotel, Athens.

President: J. V. Johannessen
Secretary: S. Fallenius
Members present: 115 members of the Society.

6. The President informed about the forthcoming European Congresses of Pathology; the next one will be held in Prague early in September, 1987. Dr. Serras then invited the European Society of Pathology to the XIIth Congress to be held in the city of Porto, Portugal, September, 1987. Then, Dr. Feriuga offered an invitation to the XIIIth Congress of the Society to be held in Ljubljana, Yugoslavia, in 1991. Both these invitations were unanimously accepted.

The President — The Secretary

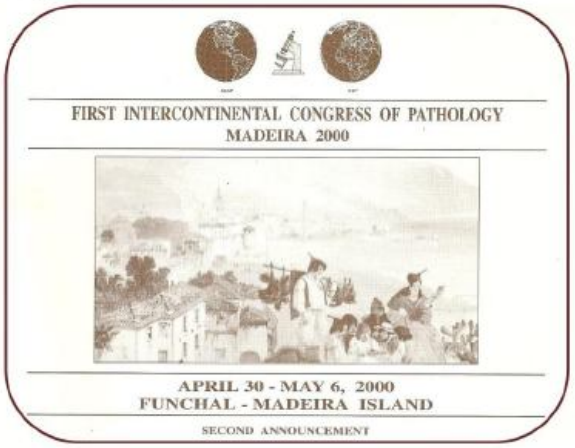
continues on p.5

European Society of Pathology

Pathology newsletter

Continues from p. 4

Fig. 4 – Second announcement of the First Intercontinental Congress of Pathology



25th European Congress of Pathology

Lisbon, August 31 – September 4, 2013

News from the FADO front

We knew the European Society of Pathology was powerful but we must confess we did not know it was SO powerful.

After having decided that FADO would be the *leit-motiv* of the Opening Ceremony at the Lisbon Congress of Pathology (August 31, 2013) it was very nice to acknowledge that FADO had been nominated by UNESCO, in the Meeting held in BALI, in November 27, 2011, as Intangible Cultural Heritage of Humanity.

It is a pity FADO is not written PHADO because it would bring an additional P to the Seven **P**s Congress. The Lisbon Congress would turn into the Eight **P**s Congress:

Pathology after **P**rague
Prognosis
Predictive
Personalized
Portugal, **P**leasure and **P**hado

The performer of the Opening Ceremony will be one of the most famous portuguese "fadistas" – CARMINHO.

European Society of Pathology

Pathology newsletter

Analecta Medica
Dr. Loukas Kaklamanis

1) Fibulin-3 as a Blood and Effusion Biomarker for Pleural Mesothelioma

Harvey I. Pass, M.D., Stephen M. Levin, M.D., Michael R. Harbut, M.D., Jonathan Melamed, M.D., Luis Chiriboga, Ph.D., Jessica Donington, M.D., Margaret Huflejt, Ph.D., Michele Carbone, M.D., Ph.D., David Chia, Ph.D., Lee Goodglick, Ph.D., Gary E. Goodman, M.D., Mark D. Thornquist, Ph.D., Geoffrey Liu, M.D., Marc de Perrot, M.D., Ming-Sound Tsao, M.D., and Chandra Goparaju, Ph.D.

N Engl J Med. 2012;367(15):1417-27. doi: 10.1056/NEJMoa1115050.

BACKGROUND

New biomarkers are needed to detect pleural mesothelioma at an earlier stage and to individualize treatment strategies. We investigated whether fibulin-3 in plasma and pleural effusions could meet sensitivity and specificity criteria for a robust biomarker.

METHODS

We measured fibulin-3 levels in plasma (from 92 patients with mesothelioma, 136 asbestos-exposed persons without cancer, 93 patients with effusions not due to mesothelioma, and 43 healthy controls), effusions (from 74 patients with mesothelioma, 39 with benign effusions, and 54 with malignant effusions not due to mesothelioma), or both. A blinded validation was subsequently performed. Tumor tissue was examined for fibulin-3 by immunohistochemical analysis, and levels of fibulin-3 in plasma and effusions were measured with an enzyme-linked immunosorbent assay.

RESULTS

Plasma fibulin-3 levels did not vary according to age, sex, duration of asbestos exposure, or degree of radiographic changes and were significantly higher in patients with pleural mesothelioma (105±7 ng per milliliter in the Detroit cohort and 113±8 ng per milliliter in the New York cohort) than in asbestos-exposed persons without mesothelioma (14±1 ng per milliliter and 24±1 ng per milliliter, respectively; P<0.001). Effusion fibulin-3 levels were significantly higher in patients with pleural mesothelioma (694±37 ng per milliliter in the Detroit cohort and 636±92 ng per milliliter in the New York cohort) than in patients with effusions not due to mesothelioma (212±25 and 151±23 ng per milliliter, respectively; P<0.001). Fibulin-3 preferentially stained tumor cells in 26 of 26 samples. In an overall comparison of patients with and those without mesothelioma, the receiver-operating-characteristic curve for plasma fibulin-3 levels had a sensitivity of 96.7% and a specificity of 95.5% at a cutoff value of 52.8 ng of fibulin-3 per milliliter. In a comparison of patients with early-stage mesothelioma with asbestos-exposed persons, the sensitivity was 100% and the specificity was 94.1% at a cutoff value of 46.0 ng of fibulin-3 per milliliter. Blinded validation revealed an area under the curve of 0.87 for plasma specimens from 96 asbestos-exposed persons as compared with 48 patients with mesothelioma.

CONCLUSIONS

Plasma fibulin-3 levels can distinguish healthy persons with exposure to asbestos from patients with mesothelioma. In conjunction with effusion fibulin-3 levels, plasma fibulin-3 levels can further differentiate mesothelioma effusions from other malignant and benign effusions. (Funded by the Early Detection Research Network, National Institutes of Health, and others.)

2) Ovarian cancer and smoking: individual participant meta-analysis including 28 114 women with ovarian cancer from 51 epidemiological studies

Collaborative Group on Epidemiological Studies of Ovarian Cancer†

Continues on P. 7

Continues from p.6

Lancet Oncol. 2012;13(9):946-56. doi: 10.1016/S1470-2045(12)70322-4.

BACKGROUND

Smoking has been linked to mucinous ovarian cancer, but its effects on other ovarian cancer subtypes and on overall ovarian cancer risk are unclear, and the findings from most studies with relevant data are unpublished. To assess these associations, we review the published and unpublished evidence.

METHODS

Eligible epidemiological studies were identified by electronic searches, review articles, and discussions with colleagues. Individual participant data for 28 114 women with and 94 942 without ovarian cancer from 51 epidemiological studies were analysed centrally, yielding adjusted relative risks (RRs) of ovarian cancer in smokers compared with never smokers.

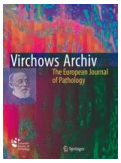
FINDINGS

After exclusion of studies with hospital controls, in which smoking could have affected recruitment, overall ovarian cancer incidence was only slightly increased in current smokers compared with women who had never smoked (RR 1·06, 95% CI 1·01—1·11, p=0·01). Of 17 641 epithelial cancers with specified histology, 2314 (13%) were mucinous, 2360 (13%) endometrioid, 969 (5%) clear-cell, and 9086 (52%) serous. Smoking-related risks varied substantially across these subtypes (pheterogeneity<0·0001). For mucinous cancers, incidence was increased in current versus never smokers (1·79, 95% CI 1·60—2·00, p<0·0001), but the increase was mainly in borderline malignant rather than in fully malignant tumours (2·25, 95% CI 1·91—2·65 *vs* 1·49, 1·28—1·73; pheterogeneity=0·01; almost half the mucinous tumours were only borderline malignant). Both endometrioid (0·81, 95% CI 0·72—0·92, p=0·001) and clear-cell ovarian cancer risks (0·80, 95% CI 0·65—0·97, p=0·03) were reduced in current smokers, and there was no significant association for serous ovarian cancers (0·99, 95% CI 0·93—1·06, p=0·8). These associations did not vary significantly by 13 sociodemographic and personal characteristics of women including their body-mass index, parity, and use of alcohol, oral contraceptives, and menopausal hormone therapy.

INTERPRETATION

The excess of mucinous ovarian cancers in smokers, which is mainly of tumours of borderline malignancy, is roughly counterbalanced by the deficit of endometrioid and clear-cell ovarian cancers. The substantial variation in smoking-related risks by tumour subtype is important for understanding ovarian carcinogenesis.

3)



Anterior gradient protein 2 (AGR2) is an independent prognostic factor in ovarian high-grade serous carcinoma

S. Darb-Esfahani[1], F. Fritzsche[2], G. Kristiansen[3], W. Weichert[4], J. Sehouli[5], I. Braicu[5], M. Dietel[1] and C. Denkert[1]

Virchows Arch. 2012;461(2):109-16. doi: 10.1007/s00428-012-1273-4.

ABSTRACT

Ovarian high-grade serous carcinoma (HGSC, type 2 ovarian carcinoma) is a poor prognosis cancer with limited therapeutic options. We aimed to investigate the expression pattern and prognostic potential of the metastasis-promoting protein anterior gradient 2 (AGR2) in primary HGSC. Immunohistochemistry was applied to a cohort of 124 primary HGSCs using tissue microarrays. Additionally, in 48 type 1 carcinomas (low-grade serous (LGSC), endometrioid (EC), clear cell (CCC), and mucinous carcinoma (MC)), AGR2 expression was investigated in an exploratory approach. A strong expression of AGR2 was seen in 15 HGSCs (12.1 %) and was significantly linked to shortened overall survival (OS, p□=□0.011) and also for progression-free survival (PFS, p□=□0.001) in the setting of adjuvant platinum-based chemotherapy (CTX). Multivariate survival analysis including age, stage, and residual tumor after surgery revealed that AGR2 expression was an independent prognostic marker for OS (p□=□0.001) and PFS (p□=□0.001) in HGSC. In type 1 carcinomas, AGR2 was significantly increased as compared to HGSC (p□=□0.001) and was seen in subsets of all histological types, low-grade serous LGSC, EC, CCC, and MC. In particular, strong diffuse staining

Continues on p.8

European Society of Pathology

Pathology newsletter

Continues from p.7

was seen in LGSC and MC. There was no association between AGR2 and estrogen receptor expression in ovarian type 1 or type 2 carcinomas.

AGR2 expression identifies highly aggressive HGSC with a compromised prognosis for which novel therapeutic options are needed. Our data strongly support the further evaluation of AGR2 as a therapeutic target and a potential marker for response to platinum-based CTX in this tumor entity.

4) Anti-VEGF antibody therapy does not promote metastasis in genetically engineered mouse tumour models‡

Singh, M., Couto, S. S., Forrest, W. F., Lima, A., Cheng, J. H., Molina, R., Long, J. E., Hamilton, P., McNutt, A., Kasman, I., Nannini, M. A., Reslan, H. B., Cao, T. C., Ho, C. C., Barck, K. H., Carano, R. A., Foreman, O., Eastham-Anderson, J., Jubb, A. M., Ferrara, N. and Johnson, L. (2012), Anti-VEGF antibody therapy does not promote metastasis in genetically engineered mouse tumour models.

J Pathol. 2012;227(4):417-30. doi: 10.1002/path.4053.

ABSTRACT

Resistance to anti-angiogenic therapy can occur via several potential mechanisms. Unexpectedly, recent studies showed that short-term inhibition of either VEGF or VEGFR enhanced tumour invasiveness and metastatic spread in preclinical models. In an effort to evaluate the translational relevance of these findings, we examined the consequences of long-term anti-VEGF monoclonal antibody therapy in several well-validated genetically engineered mouse tumour models of either neuroendocrine or epithelial origin. Anti-VEGF therapy decreased tumour burden and increased overall survival, either as a single agent or in combination with chemotherapy, in all four models examined. Importantly, neither short- nor long-term exposure to anti-VEGF therapy altered the incidence of metastasis in any of these autochthonous models, consistent with retrospective analyses of clinical

In contrast, we observed that sunitinib treatment recapitulated previously reported effects on tumour invasiveness and metastasis in a pancreatic neuroendocrine tumour (PNET) model. Consistent with these results, sunitinib treatment resulted in an up-regulation of the hypoxia marker GLUT1 in PNETs, whereas anti-VEGF did not.

These results indicate that anti-VEGF mediates anti-tumour effects and therapeutic benefits without a paradoxical increase in metastasis. Moreover, these data underscore the concept that drugs targeting VEGF ligands and receptors may affect tumour metastasis in a context-dependent manner and are mechanistically distinct from one another.

5) CTNNB1 mutation analysis is a useful tool for the diagnosis of desmoid tumors: a study of 260 desmoid tumors and 191 potential morphologic mimics

Sophie Le Guellec[1], Isabelle Soubeyran[2], Philippe Rochaix[1], Thomas Filleron[3], Agnès Neuville[2,4], Isabelle Hostein[2] and Jean-Michel Coindre[2,4]

Mod Pathol. 2012;25(12):1551-8. doi: 10.1038/modpathol.2012.115.

ABSTRACT

Desmoid tumors are benign monoclonal fibroblastic or myofibroblastic neoplasms, characterized by local invasiveness and high rates of recurrence. Desmoid tumors must be distinguished from benign fibroblastic and myofibroblastic lesions, as well as from low-grade sarcoma, which can appear histologically similar to desmoid tumors. This differential diagnosis can be very difficult, especially when diagnosis is based on a core needle biopsy. On the molecular level, most sporadic desmoid tumors are associated with mutations of the *β*-catenin gene (*CTNNB1*). A minority of desmoid tumors are associated with Gardner syndrome and mutations of the familial adenomatous polyposis gene. We identified the common *CTNNB1* mutations associated with sporadic desmoid tumors by direct sequencing: in (i) 260 cases of typical desmoid tumors; and (ii) in 191 cases of spindle cell lesions, which can morphologically 'mimic' desmoid tumors. Formalin-fixed paraffin-embedded tissues were obtained via core needle biopsy (*n*=150) or open biopsy/surgical excision (*n*=301).

Continues on p.9

Continues from p.8

Only 16 cases (4%) were not analyzable (Bouin's fixed tissue). *CTNNB1* mutations were observed in 223 of 254 (88%) of sporadic desmoid tumors. No *CTNNB1* mutations were detected in all other lesions (*n*=175) studied. *CTNNB1* sequencing can be easily and reliably done using tissues obtained via core needle biopsy.

Detection of *CTNNB1* mutations in formalin-fixed paraffin-embedded tissues among spindle cell lesions is proposed as a specific diagnostic tool for the diagnosis of desmoid tumors. This result has significant implications for patient care and management.

6) 

Reproducibility of histopathological subtypes and invasion in pulmonary adenocarcinoma. An international interobserver study

Erik Thunnissen[1], Mary Beth Beasley[2], Alain C Borczuk[3], Elisabeth Brambilla[4], Lucian R Chirieac[5], Sanja Dacic[6], Douglas Flieder[7], Adi Gazdar[8], Kim Geisinger[9], Philip Hasleton[10], Yuichi Ishikawa[11], Keith M Kerr[12], Sylvie Lantejoul[4], Yoshiro Matsuno[13], Yuko Minami[13], Andre L Moreira[14], Noriko Motoi[11], Andrew G Nicholson[15], Masayuki Noguchi[13], Daisuke Nonaka[16], Giuseppe Pelosi[17], Iver Petersen[18], Natasha Rekhtman[14], Victor Roggli[19], William D Travis[14], Ming S Tsao[20], Ignacio Wistuba[21], Haodong Xu[22], Yasushi Yatabe[23], Maureen Zakowski[14], Birgit Witte[24] and Dirk Joop Kuik[24]

Mod Pathol. 2012;25(12):1574-83. doi: 10.1038/modpathol.2012.106.

ABSTRACT

Histological subtyping of pulmonary adenocarcinoma has recently been updated based on predominant pattern, but data on reproducibility are required for validation. This study first assesses reproducibility in subtyping adenocarcinomas and then assesses further the distinction between invasive and non-invasive (wholly lepidic) pattern of adenocarcinoma, among an international group of pulmonary pathologists. Two ring studies were performed using a micro-photographic image-based method, evaluating selected images of lung adenocarcinoma histologic patterns. In the first study, 26 pathologists reviewed representative images of typical and 'difficult' histologic patterns. A total number of scores for the typical patterns combined (*n*=94) and the difficult cases (*n*=21) were 2444 and 546, respectively. The mean kappa score (±s.d.) for the five typical patterns combined and for difficult cases were 0.77±0.07 and 0.38±0.14, respectively. Although 70% of the observers identified 12–65% of typical images as single pattern, highest for solid and least for micropapillary, recognizing the predominant pattern was achieved in 92–100%, of the images except for micropapillary pattern (62%). For the second study on invasion, identified as a key problem area from the first study, 28 pathologists submitted and reviewed 64 images representing typical as well as 'difficult' examples. The kappa for typical and difficult cases was 0.55±0.06 and 0.08±0.02, respectively, with consistent subdivision by the same pathologists into invasive and non-invasive categories, due to differing interpretation of terminology defining invasion.

In pulmonary adenocarcinomas with classic morphology, which comprise the majority of cases, there is good reproducibility in identifying a predominant pattern and fair reproducibility distinguishing invasive from *in-situ* (wholly lepidic) patterns. However, more precise definitions and better education on interpretation of existing terminology are required to improve recognition of purely *in-situ* disease, this being an area of increasing importance.

7) 

Effect of the MDM2 antagonist RG7112 on the P53 pathway in patients with MDM2-amplified, well-differentiated or dedifferentiated liposa-rcoma: an exploratory proof-of-mechanism study

Dr Isabelle Ray-Coquard MD a b, Prof Jean-Yves Blay MD a c, Antoine Italiano MD d, Axel Le Cesne MD e, Nicolas Penel MD f, Jianguo Zhi PhD g, Florian Heil PhD h, Ruediger Rueger MD h, Bradford Graves PhD g, Meichun Ding PhD g, David Geho MD g, Steven A Middleton PhD g, Lyubomir T Vassilev PhD g, Gwen L Nichols MD g, Binh Nguyen Bui MD d

Lancet Oncol. 2012;13(11):1133-40. doi: 10.1016/S1470-2045(12)70474-6.

BACKGROUND

We report a proof-of-mechanism study of RG7112, a small-molecule MDM2 antagonist, in patients with chemotherapy-naive primary or relapsed well-differentiated or dedifferentiated *MDM2*-amplified liposarcoma who were eligible for resection.

Continues on p. 10

European Society of Pathology

Pathology newsletter

Continues from p.9

METHODS

Patients with well-differentiated or dedifferentiated liposarcoma were enrolled at four centres in France. Patients received up to three 28-day neoadjuvant treatment cycles of RG7112 1440 mg/m2 per day for 10 days. If a patient progressed at any point after the first cycle, the lesion was resected or, if unresectable, an end-of-study biopsy was done. The primary endpoint was to assess markers of RG7112-dependent MDM2 inhibition and P53 pathway activation (P53, P21, MDM2, Ki-67, macrophage inhibitory cytokine-1 [MIC-1], and apoptosis). All analyses were per protocol. This trial is registered with EudraCT, number 2009-015522-10.

RESULTS

Between June 3, and Dec 14, 2010, 20 patients were enrolled and completed pretreatment and day 8 biopsies. 18 of 20 patients had *TP53* wild-type tumours and two carried missense *TP53* mutations. 14 of 17 assessed patients had *MDM2* gene amplification. Compared with baseline, P53 and P21 concentrations, assessed by immunohistochemistry, had increased by a median of 4·86 times (IQR 4·38—7·97; p=0·0001) and 3·48 times (2·05—4·09; p=0·0001), respectively, at day 8 (give or take 2 days). At the same timepoint, relative *MDM2* mRNA expression had increased by a median of 3·03 times (1·23—4·93; p=0·003) that at baseline. The median change from baseline for Ki-67-positive tumour cells was −5·05% (IQR −12·55 to 0·05; p=0·01). Drug exposure correlated with blood concentrations of MIC-1 (p<0·0001) and haematological toxicity. One patient had a confirmed partial response and 14 had stable disease. All patients experienced at least one adverse event, mostly nausea (14 patients), vomiting (11 patients), asthenia (nine patients), diarrhoea (nine patients), and thrombocytopenia (eight patients). There were 12 serious adverse events in eight patients, the most common of which were neutropenia (six patients) and thrombocytopenia (three patients).

DISCUSSION

MDM2 inhibition activates the P53 pathway and decreases cell proliferation in *MDM2*-amplified liposarcoma. This study suggests that it is feasible to undertake neoadjuvant biopsy-driven biomarker studies in liposarcoma.

Dr. Loukas Kaklamanis

What's new?

Revealing the secrets of Alzheimer's Disease: The Beginning of the End?

Dr. Loukas Kaklamanis

A fascinating study published online in November 14, 2012 at the N.Engl. J.Med by *T. Jonsson, H. Stefansson et al* under the title "Variant of TREM2 associated with risk of Alzheimer's disease". Their findings strongly implicates a variant in the gene encoding the triggering receptor 2 expressed on myeloid cells (TREM2) In the pathogenesis of Alzheimer''s disease (AD).

The majority of known genome sequence variants importantly associated with the risk for AD,include PSEN1,PSEN2 and APP, which encode respectively presenillin 1, presenillin 2 and the amyloid precursor protein. But these variants are related to early-onset AD and not to the much common late-onset one. The most important late-onset related genome sequence variant so far, is that of the ε4 allele of apolipoprotein E.

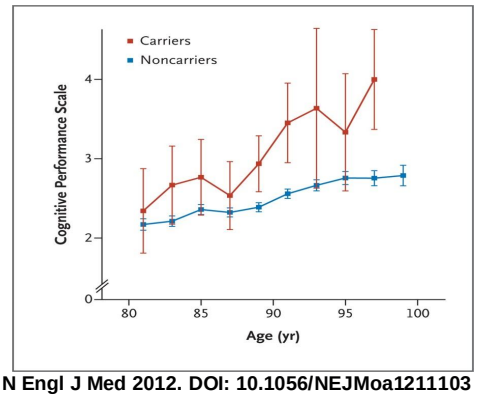
The researchers obtained the genome sequences of 2261 Icelanders trying to identify variants which are likely to influence protein function. They manage to identify a rare missense mutation (rs75932628-T) in the gene encoding TREM2 which causes an R47H. This missence mutation was associated with almost tripple the risk for AD in the Icelandic cohort (OR 2.92,;95%CI,2.16-3.91; $P=2.1x10^{-10}$).
Elderly people (80-100 years of age) who did not have AD, but were carriers of the rs75932628-T mutation, had poorer cognitive functions compared to non-carriers. This mutation is less frequent than that of the apolipoprotein E ε4 allele but it confers a similarly strong effect ApoE ε4.

They also performed replication tests using case-control series from Emory (USA), Rotterdam (NL),Munich (Germany) and Norway. The association of this mutation with AD was remarkably highly significant too.

Cognition as a Function of Age in Controls Who Were Carriers or Noncarriers of the rs75932628-T Variant Associated with the Risk of Alzheimer's Disease.

Continues on p.11

Continues from p.10

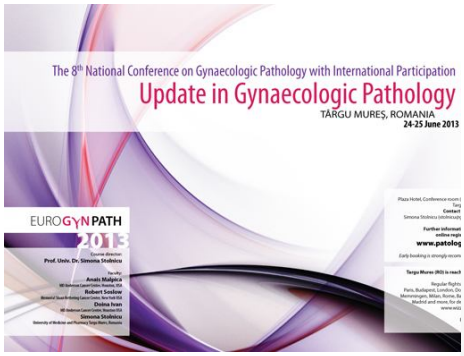


Jonsson T et al. N Engl J Med 2012. DOI: 10.1056/NEJMoa1211103

Figure 1. Shown are scores on the Cognitive Performance Scale(CPS) for carriers and noncarriers of the rs75932628-T variant associated with Alzheimer's disease, according to age. Scores on the CPS range from 0 to 6, with higher scores indicating more severe impairment. Values are shown in 2-year bins (i.e., the data point for 81 years of age contains data for ages 80 and 81), except for the last bin, which represents ages of 98, 99, and 100 years. No CPS data were available for carriers in the last age bin. Each data point represents the average CPS score for participants in the respective age bin. The I bars represent standard errors. The graph is based on 307 measurements from 53 carriers and 24,152 measurementsfrom 3699 noncarriers. Patients in whom Alzheimer'sdisease had been diagnosed were not included in th analysis.

TREM2 is a transmembrane glycoprotein expressed by microglial cells and has been implicated in anti-inflammatory action in the brain. The identified missense mutation may increase the inflammatory processes resulting in increase predisposition to AD. TREM2 is also implicated in the phagocytic role of the microglial cells on amyloid plaques. Decreasing this activity neuronal damage could be caused due to inability of the brain to clear toxic molecules.
In an interview to Megan Brooks from Medscape Medical News both Dr.Stefansson (the cief investigator) and Dr.Ties (Chief scientific Officer ,AD Assosiation), reveiled that: "TREM2 is an attractive target for drug development."Dr. Thies said, "We've known for some time that inflammation is associated with Alzheimer's disease but we haven't really been able to exploit that with current drugs. The nonsteroidal anti-inflammatory drugs have sort of a checkered history in being useful for Alzheimer's disease."

"This kind of genetic study with whole genome sequencing that points to a very specific gene that is attached to a metabolic pathway really opens up the possibility of finding molecules that will work to modulate that pathway to a clinical benefit."



http://www.patologia.ro/manifestari.html

2nd Edinburgh-Haematopathology Tutorial: "Rare entities; Age- and immunosupression-related lymphoproliferations". Edinburgh, May 23-24, 2013.

www.edinburgh-haematopathology.org.uk

European Society of Pathology

Pathology newsletter

EScoP Ankara, 11th until 13th October 2012

Ass. Prof. Duygu Kankaya & Prof. Ayşe Sertçelik

Dear Colleagues,

EScoP Ankara branch held a Gynaecopathology course in the Department of Pathology, Ankara University Medical School between 11-13th October, 2012. The faculty comprised of three experienced gynaecopathologists from the UK; Prof. Mike Wells (Sheffield), Dr. Lynn Hirschowitz (Birmingham), Dr. Raji Ganesan (Birmingham). There were 60 participants; 51 from Turkey, 3 from Georgia, 2 from St-Petersburg, 1 from Egypt, 1 from Iran, 1 from Belgium, and 1 from Sweden. Lectures, followed by slide seminars and videomicroscopy sessions on the hot topics of gynaecopathology were successfully presented by the faculty members and were very well received by the participants. This fruitful three-day long course ended with a short walk in the castle area followed by a gala dinner in a historical museum. The feedback from the participants was excellent encouraging us to continue hosting EScoP courses in Ankara.

We are grateful to the faculty for their precious time and efforts for such a successful course. We also thank the participants for their attendance and valuable feedback.

We hope to meet you all again in the future EScoP courses to be held in Ankara.

Best wishes,

Ass. Prof. Duygu Kankaya & Prof. Ayşe Sertçelik

Pictures from EScoP Ankara 2012

Picture 1 : Gala Dinner with Drs. Ganesan and Hirschowitz and the participants.

Picture 2: The participants with Prof. Mike Wells on the third day of the course.

European Society of Pathology

Pathology newsletter

Pathology Meets Gastroenterology

Prof. Cord Langner, Prof. Valerie Paradis, Prof. Dina Tiniakos

About one year ago ESP initiated a formal negotiation process aiming at official partnership with „United European Gastroenterology“ (UEG) which serves as a non-profit organization combining all the leading European societies concerned with digestive diseases.

This year UEG celebrated 20 years since the first of the annual meetings, now known as the UEG Week. The birthday event of the 20th UEG Week which took place on October 20-24 in Amsterdam marked by record numbers: With over 14,000 delegates from 125 countries attending the meeting, the UEG Week in Amsterdam had the best turnout in UEG history.

It was a great honour for the Working Group of Digestive Diseases (WG-DD) of ESP to organize a multidisciplinary session at UEG Week which attracted more than 1,000 participants:

“Endoscopy meets pathology: Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD)”

1. EMR and ESD in the upper GI tract (Horst Neuhaus, Germany)
2. The pathologist’s role in the evaluation of upper GI tract EMR/ESD-specimens (Cord Langner, Austria)
3. Molecular pathogenesis of upper GI carcinoma: What the clinician needs to know (Ari Ristimäki, Finland)
4. EMR and ESD in the lower GI tract (Bjorn Rembacken, United Kingdom)
5. The pathologist’s role in the evaluation of lower GI tract EMR/ESD-specimens (Michael Vieth, Germany)
6. Molecular pathogenesis of lower GI carcinoma: What the clinician needs to know (Inti Zlobec, Switzerland)

Every year the UEG National Societies Committee and the Scientific Committee jointly select up to eight emerging clinical scientists at UEG Week. Those young researchers are awarded “Rising Star Status” based on a track record of international-quality research.

This year, Dr. Iris Nagtegaal (Nijmegen, The Netherlands), member of WG-DD, was awarded “Rising Star Status” and gave a lecture on “Evidence based treatment decisions in colorectal cancer: The role of the pathologist“.

In all, nine members of WG-DD actively participated in the gastrointestinal and hepatobiliary scientific program of UEG Week as course directors, chairpersons, speakers, experts in clinical case multidisciplinary sessions and/or poster judges and we hope that this number will increase in the following years.

For 2013, we are happy to announce the first Joint ESP / UEG Joint Symposium on the occasion of our annual congress in Lisbon. The topic will be “Metaplasia”, and two leading European gastroenterologists have been approached to give lectures in this interdisciplinary session.

Prof. Valerie Paradis and Prof. Cord Langner

ESP session at UEGW: Endoscopy meets pathology.

European Society of Pathology

Pathology newsletter

The 29th IUCP in Ioannina in April 2012

Prof. Niki Agnantis

The 29th postgraduate IUCP on LIVER Pathology-Oncology (part one) and (part two) was held in Ioannina, Hellas, between April 24th and 27th, 2012.

The course was very successful, according to the evaluation of the questionnaires and the 37 students along with the 25 Faculty members enjoyed this fruitful Scientific Event.

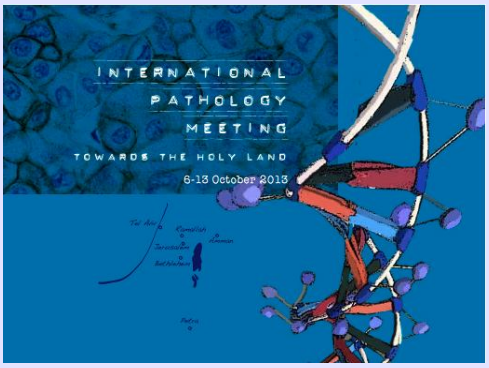
Since the course belongs to the second series of IUCP (the first one was held on May 1998), we honored the members of the Faculty who contributed immensely to the success of the 1st course, which was also dedicated exclusively in LIVER Pathology-Oncology. Our Honorary Guests were the following on alphabetical basis: C.Barbatis, J.Delladetsima, M.Demonakou, P.Hytiroglou, L.Pollice, B.Portmann, D.G.Tiniakos, M.G.Tiniakos, and E.Tsianos.

Besides Science, everybody enjoyed the every evening social events and especially the farewell dinner held at the georgious "Hotel du Lac'' with music and dance until early morning!! The 29th IUCP belongs to history and now I am very pleased to announce to the ESP members the forthcoming 30th IUCP on Breast Pathology-Oncology , which will be held in Ioannina, Hotel "Palladion" between the 28th and the 31st of May 2013. For further information, our ESP members can visit the IUCP website after January 20th, 2013.

Institute of Pathology Charité - Universitätsmedizin Berlin

Lecture Hall 20th March 2013

http://www.dgp-berlin.de/downloads/public/invitations/2012-11-13_Pre-Alalytic-Symposium-2013.pdf



http://www.ipm-holyland.com

European Society of Pathology

Pathology newsletter

Grotto of Serralves Garden, Porto, Portugal
(Photo of Jose Paulo Andrade)

Dear Colleague

Looking forward to the next European Congress of Pathology in Lisbon, we wish you a Merry Christmas and a prosperous New Year.

We hope that your ESP membership will also bring you great personal and professional satisfaction in 2013.

The ESP Executive Committee officers:

Fátima Carneiro, ESP President
Han van Krieken, ESP President-elect
Ilmo Leivo, ESP Secretary
Marco Santucci, ESP Treasurer
Michael Wells, ESP Past-President

Krasi Serguieva, ESP Administrator