ARTICLE |
THE PROGNOSTIC SIGNIFICANCE OF BRAF MUTATIONS IN PATIENTS WITH MELANOMA

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The Amsterdam Medical Student journal (AMSj) is a scientific journal created and published by Amsterdam UMC staff members and students to promote research and to encourage other medical students to publish their clinical observations, research articles and case reports. Go to www.amsj.nl for publication options and to find out how you can contribute to AMSj as reviewer or member of the editorial board.

Editorial

On behalf of the editorial board I would like to welcome you to the first edition of AMSj in this new decade. Moreover, publishing in multiple decades is not the only milestone in this edition: AMSj has also now been publishing for over five years. Much like the passing of a decade is perceived by many as a moment of change, AMSj has changed a lot over the years. We have seen many improvements over the years, both in our fixed content as well as in the articles that are submitted to AMSj. As Editor-in-Chief, I feel compelled to thank all of the contributors to AMSj for continually providing us with engaging content.

In the coming decade, we hope to keep evolving as a medical journal, and more change is coming. Firstly, we are pleased to welcome new staff and student reviewers for specialties, as well as a new creative editor and several new general board members. I too am excited to be the incoming Editor-in-chief AMC, taking up the mantle from Rens Kempeneers. Although I and all of the new reviewers, editors and board members are thrilled to use this opportunity to contribute to AMSj and learn from this experience, we will miss the expertise of the retiring contributors and we would like to thank them for their commitment to AMSj.

Secondly, we are happy to share that we have been working on exciting new collaborations with several enterprises, including Medical Business Course, the Association Surgery for Medical Students (also known as *Vereniging Chirurgie voor Medisch Studenten or VCMS*) and VGT Cursus. With these collaborations, we hope to create not only appealing new content, but also new opportunities for our readers.

Although much has indeed changed in the last five years and much will change in the future about AMSj, our main goal has always been the same. With each new edition, we hope to stimulate the conduct of research among our readership, provide the opportunity to publish research, opinion pieces and interviews, and allow our contributors to achieve new scientific and writing skills in an accessible way. I hope we will be able to strive for these goals for at least another decade.

Please enjoy the 18th edition of AMSj,

Devica S. Umans
Student Editor-in-Chief
Amsterdam UMC,
location AMC

NEWSNEWSNEWS

Using artificial intelligence: is “Barrett” a lesser threat?

K. de Wit[1] and T. van Ramshorst[1]
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Barrett’s esophagus (BE) is a condition of the esophagus where the normal cell lining is replaced by abnormal cells, often due to reflux esophagitis. Barrett’s esophagus is associated with an increased risk of esophageal adenocarcinoma. Currently, high definition white light endoscopy is used by endoscopists to perform endoscopic surveillance in patients with BE and detect early neoplasia. However, early detetion still fails occasionally. In a recent new study, conducted by the Eindhoven University of Technology and centers for Barrett esophagus referrals in The Netherlands, a deep learning computer aided system (CAD) was developed and validated.[1] This system detects neoplasia in patients with BE, achieving higher accuracy than endoscopists, and is based on artificial intelligence. It was developed using 1704 high resolution images of early neoplasia and non-dysplastic esophagus, in which it can recognize patterns of neoplasia in images and simultaneously produce a heatmap with corresponding delineation in any neoplastic image. Eventually, two external datasets were assessed by the CAD system and general endoscopists. The CAD system achieved better outcomes than general endoscopists in accuracy (88% vs 73%), sensitivity (93% vs 72%) and specificity (83% vs 74%). These results are promising for future diagnostics of early neoplasia in BE patients.

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To screen or not to screen

Johanna da Silva Voorham[1] and Anna Emanuel[2]
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2. Department of Internal Medicine, Amsterdam UMC, Location AMC

Since the introduction of population-based breast cancer screening, breast cancer-related mortality has significantly decreased, which may partly result from early detection.[1] Currently, controversy exists about whether or not additional screening is desired to reduce false negative findings in high risk groups, e.g. women with extremely dense breast tissue. High breast density limits the detection of cancer by mammography, increasing the false negative risk.[2] The Dense Tissue and Early Breast Neoplasm Screening (DENSE)-trial was a multicenter randomized controlled trial on supplemental MRI screening for women with extremely dense breast tissue.[3] The primary outcome was the rate of interval cancers, which was significantly lower in the women who were subjected to an additional MRI. However, data on interval cancer rate should not be interpreted as survival data. In addition, increasing sensitivity with additional tests inevitably leads to high false positive rates, overdiagnosis, high medical costs and negative psychological impact. Therefore, longer follow-up is needed to assess the effect on the rate of advanced cancers and on cancer-related and overall mortality before supplemental MRI screening should be implemented nationwide.

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2. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2006;15(6):1159-69.
3. Bakker MF, de Lange SV, Pijnappel RM, et al.Supplemental MRI Screening for Women with Extremely Dense Breast Tissue. N Engl J Med. 2019;381(22):2091-102.

Uncomplicated late term pregnancies: induction of labor versus expectant management

Charlotte Leseman[1] and Jan Molkenboer[2]
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2. Department of Gynecology & Obstetrics, Spaarne Gasthuis, Haarlem

The risk of adverse perinatal outcomes rises after 40 weeks of pregnancy. Previous studies have shown that perinatal outcomes improve by induction of labor from 41 weeks onwards.[1] In the Netherlands expectant management until 42 weeks is standard in low risk pregnancies, although there is wide variation in practice.[2] Keulen et al. included 1801 women with low risk, uncomplicated pregnancies and randomized them for either induction of labor at 41 weeks or expectant management until 42 weeks.[3] Primary outcomes were defined as perinatal mortality (e.g. fetal death) and neonatal morbidity (e.g. Apgar score <7 at five minutes). 15/900 women (1.7%) in the induction group versus 28/901 women (3.1%) in the control group had an adverse perinatal outcome (p=0.22). In this study induction, at 41 weeks, resulted in less overall adverse perinatal outcomes compared to expectant management until 42 weeks. However, in both groups the absolute risk of severe adverse outcomes was low. These results should be used for counseling women approaching 41 weeks of pregnancy so that they can decide whether they prefer induction or to await spontaneous labor.

1. Middleton P, Shepherd E, Crowther CA. Induction of labour for improving birth outcomes for women at or beyond term. Cochrane Database Syst Rev 2018;5:CD004945.
2. Nederlandse Vereniging voor Obstetrie & Gynaecologie. Guideline Prolonged Pregnancy. Serotiniteit, 2007.
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The antidepressant effect of anti-inflammatory agents

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2. Department of Psychiatry, Amsterdam UMC, location AMC

The pharmacological management of major depressive disorder (MDD) is largely based on neurotransmitter targeting. However, adverse effects are frequently reported and an estimate of 30% of MDD patients remain therapy-refractory. Recent research has shown that people with MDD have increased levels of inflammatory markers. This finding raises the question whether anti-inflammatory agents could be used to treat depressive symptoms in people with MDD. Hence, Bai et al compared the efficacy and safety of anti-inflammatory agents against a placebo for patients with MDD in a systematic review and meta-analysis.[1] Thirty randomized placebo-controlled trials with 1610 participants were included in the quantitative analysis. The intervention group received treatment with an anti-inflammatory agent, either as monotherapy or combined with antidepressants. The primary outcome was change in depression severity. The intervention group reported significantly lower scores on depression rating scales than the placebo group, as well as higher response and remission rates. The most effective anti-inflammatory agents were NSAIDs, omega-3 fatty acids, statins and minocyclines. Furthermore, adjunctive treatment was more effective than monotherapy. Participants using statins or N-acetylcysteine reported more minor gastrointestinal events than the placebo group. This was the only significant adverse event. In conclusion, anti-inflammatory agents have a significant antidepressant effect and are considered safe for the treatment of patients with MDD. Considering the chronicity of MDD, future research should focus on long-term efficacy of this treatment.

1. Bai, S., Guo W, Feng Y, et al. Efficacy and safety of anti-inflammatory agents for the treatment of major depressive disorder: a systematic review and meta-analysis of randomised controlled trials. J Neurol Neurosurg Psychiatry. 2020. 91(1), 21–32. doi: 10.1136/jnnp-2019-320912

H.L. Tan, MD, PhD

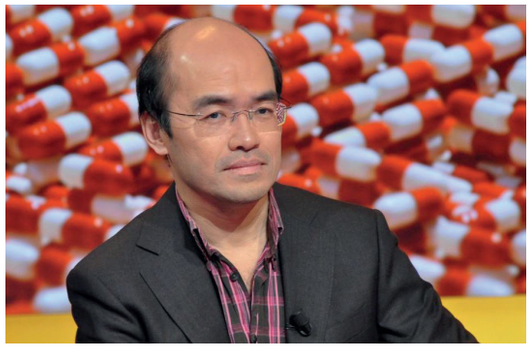
Interviewed by Salina Novin[1]
1. Faculty of Medicine, Amsterdam UMC, location AMC, University of Amsterdam, Amsterdam

Area of expertise:
Cardiac electrophysiology and arrhythmia

Current position:
- Staff member, Department of Cardiology and Laboratory of Experimental Cardiology Amsterdam UMC, Location AMC
- Principal Investigator Amsterdam UMC, Location AMC

Publications: 200 papers

How did you become involved in Cardiology?
I had the good fortune to be immediately fascinated by the electrical properties of the heart very early on during my medical studies at the UvA. This gave me focus and guidance. I remember vividly attending one of my first Physiology lectures in week 6 of year 1. Professor Lennart Bouman lectured about the cardiac action potential and I was immediately awestruck by the logic and elegance of the system underlying it. I knew there and then that I wanted to spend my time studying the heart and working on research and treatment of cardiac arrhythmia. I was also fortunate that the Department of Cardiology of AMC was a world-renowned institution for research into cardiac arrhythmia and that Professor Giel Janse of the Laboratory of Experimental Cardiology offered me a PhD student position immediately after I graduated as an MD. After finishing my PhD there, I was trained and worked as a staff cardiologist at AMC, and had the good fortune to always find myself in a highly stimulating environment in which I could combine science and clinical work in cardiac arrhythmia. Experiences in other laboratories (1 year at Stanford University USA, 1 year at Vanderbilt University USA, and 1 year at the research labs of drug companies in Switzerland and Japan) further broadened my scope and were highly inspiring and enjoyable.



Dr. H.L. Tan

CURRICULUM VITAE

1982-1989	Medical School University of Amsterdam
1989-1993	PhD student Laboratory of Experimental Cardiology AMC
1993	PhD thesis 'Cellular electrical uncoupling and protection of ischemic myocardium'
1993-1994	Postdoc, Cardiac Electrophysiology and Arrhythmia Service, Stanford University Medical Center, Stanford USA
1994-2000	Cardiologist-in-training, AMC
2000	Registration as Cardiologist
2000	Postdoc, Department of Anesthesiology and Pharmacology, Vanderbilt University Medical Center, Nashville USA
2001-present	Staff member, Department of Cardiology and Laboratory of Experimental Cardiology AMC
2007-present	Principal Investigator AMC

What are your research interests?
Cardiac electrophysiology, arrhythmia and sudden cardiac arrest are the general focus. However, my interest is wider than average. I very much enjoy studying these subjects in a comprehensive fashion. My other interests include: clinical science, epidemiology, basis science (cellular electrophysiology, genetics), neuroscience, public health and ethics.

Did you always have the ambition to become a cardiologist?
I decided only in the final year of my graduate studies to also become and work as a clinical cardiologist.

How do you split your time between clinical practice and research?
I did a 50/50 split for the first 20 years of working as a cardiologist in AMC, but have recently moved almost exclusively to research.

Do you have any further ambitions?
Enjoy the good things that life offers and always remain curious and open-minded.

Do you think that performing medical research is a requirement to become a good doctor?
Absolutely, but the reverse is also true: this is a classic example of the sum far exceeding the value of its constituent parts.

Which scientific finding or publication are you most proud of?
There are many achievements that I am happy I was a part of, and it is difficult to point out single achievements. Two publications that probably do stick out are a pair of Nature papers on cellular electrophysiological work (patch-clamp) that I did myself when I was already a cardiologist.

What would your advice be to medical students?
Do what your heart tells you to do. Strive to combine science and clinical work.

> "Do what your heart tells you to do"

VGT Giveaway

VGT Cursus

VGT Cursus awarded a FlexPack course to the winning manuscript of edition 19, including the VGT Handbook & E-learning (both in Dutch). This manuscript will be published in the next edition of AMSj. Follow our social media channels for future giveaways!

QUESTION 1

An 81-year-old man living independently has developed a fear of falling after having fallen once in the past year, resulting in him staying at home more often. Which risk factor contributes most in predicting future falls in this patient?

A. Fear of falling
B. His past fall
C. Age above 80 years

Insufficient evidence exists to state that fear of falling is an independent and significant risk factor for future falls. There is also no evidence that reducing fear of falling leads to a reduced fall incidence. The association between falling and fear of falling seems to be mediated by other factors, e.g. fear of falling leads to reduced physical activity, which in turn leads to increased fall risk. By contrast, a past fall will in fact increase the risk of falling in the future (OR 1,2-3,3). This risk increases as the number of past falls increases.

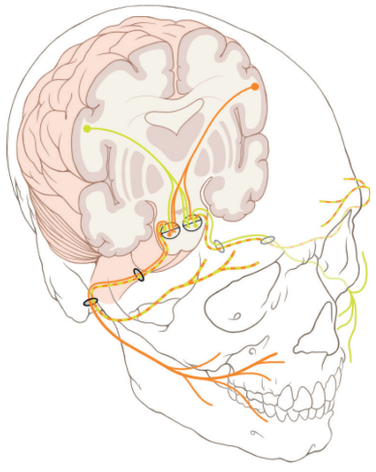
EXPLANATION

Answer: B

QUESTION 2

A patient presents with atraumatic loss of function of several facial muscles. His left mouth corner protrudes low compared to the right side and he is unable to fully close his left eye. Which nerve is most likely damaged?

A. Left central facial nerve
B. Right central facial nerve
C. Left peripheral facial nerve
D. Right peripheral facial nerve



In a central facial palsy, the contralateral m. orbicularis oculi, which closes the upper eyelid, is spared since the muscles in the upper half of the face are innervated bilaterally. In a peripheral facial palsy, the ipsilateral m. orbicularis oculi is affected, as is the entire ipsilateral facial musculature. See figure below for a schematic representation.

EXPLANATION

Answer: B

Headache and blurry vision

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2. University of Amsterdam, Amsterdam UMC, Amsterdam Neuroscience, Department of Neurology

CASE

A 60-year-old female known with migraine without aura and multiple dental surgeries in the past, presented with fever and severe frontal headache after a few weeks of flu-like symptoms. The symptoms accompanied blurry vision which gradually progressed into a complete loss of the right visual field of both eyes. Physical and neurological examination showed no other abnormalities. Biochemistry revealed a minimal raise of leukocyte count 11.8 and a slight increase of erythrocyte sedimentation rate (ESR) 30. A MRI cerebrum was performed and is shown on the right.

QUESTION 1

What is the correct order of the MRI sequences?

A. T1 with contrast, T2, DWI and ADC
B. T1 with contrast, T2, ADC and DWI
C. T2, T1 with contrast, ADC and DWI
D . 2, T1 with contrast, DWI and ADC

Hint: For each MRI sequence, try to compare the signal (hypointense = black, hyperintense = white) of the cerebrospinal liquor to the signal of the lesion.

QUESTION 2

What is the most likely diagnosis based on clinical presentation and MRI?

A . Cerebral abscess
B. High-grade glioma
C. Subacute hemorrhage
D. Subacute infarction

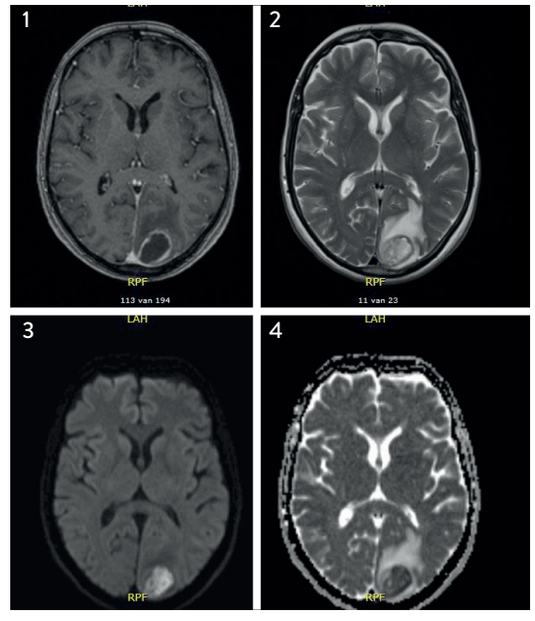
Hint: Diffusion weighted sequences showing central diffusion restriction is a critical finding for suggesting the diagnosis

QUESTION 3

What is the medical term for the visual field abnormality described in the case?

A. Bitemporal hemianopsia
B. Monocular vision loss
C. Heteronymous hemianopsia
D. Homonymous hemianopsia

Hint: Which part of the optical nerve pathway is affected by the cerebral lesion visible on MRI?



Answer on page 21

The prognostic significance of BRAF mutations in patients with melanoma

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2. Department of Pathology, University Clinical Centre of the Republic of Srpska, Bosnia and Herzegovina

ABSTRACT

INTRODUCTION Melanoma is a malignant skin tumor of melanocytic cells' origin, which has high tendency for metastasis. Determination of presence of BRAF mutations plays an important role in the application of targeted chemotherapy. The primary aim of our study was to determine impact of targeted therapy on duration of the disease (overall survival - OS). Prevalence of BRAF mutations, as well as pathohistological characteristics were also analysed.

METHODS This retrospective study included 30 patients treated for metastatic melanoma at University Clinical Centre of the Republic of Srpska (UCCRS). Detection of BRAF V600 mutation was performed by Real-time polymerase chain reaction (RT-PCR) method, Cobas 4800 System, Cobas BRAF mutation test at the Department of Pathology UCCRS from 2014 to 2018. Data were obtained concerning pathohistological and oncological findings, by accessing medical records from Clinical Informational System.

RESULTS Out of 30 in total, there were 17 (56.7%) BRAF positive tumors and 13 (43.3%) BRAF negative. BRAF positive tumors occurred at an earlier age (median 51.0 years vs. BRAF negative 63.0 years). Median OS for all BRAF positive patients was 20.0 months, whereas BRAF negative patients, treated with standard chemotherapy, had OS of 25.0 months. Among BRAF positive tumors, patients in metastatic advanced disease treated with vemurafenib (N=10.0) had a longer OS (40.0 months) than BRAF positive patients treated with standard chemotherapy (N=7.0) (OS 16.0 months). Tumors were most commonly diagnosed in the pT4 stage (51.8%), of nodular type (85.2%) and with a median Breslow thickness of 3.3 mm.

CONCLUSION Our study showed that treatment with vemurafenib improves OS in BRAF positive patients, which is in line with other clinical studies. BRAF positive tumors occurred at an earlier age, and without targeted therapy, had shorter OS than BRAF negative tumors treated with standard chemotherapy.

INTRODUCTION

Melanoma is a malignant skin tumor of melanocytic cells' origin, which has an aggressive course and a high tendency for metastasis. Metastatic disease has a survival time of less than one year.[1] The use of cisplatin and dacarbazine (CDDP/DTIC) in standard metastatic disease chemotherapy did not significantly prolong the survival of patients with advanced disease.[2]

An important clinical-pathological parameter is Breslow thickness – tumor thickness in the vertical phase of growth expressed in mm. Thinner Breslow depth indicates a smaller chance that the cancer has spread.[3]

BRAF is a sporadic serine/threonine kinase activation mutation, that occurs in about 60% of melanoma but also in other cancers, including colorectal cancer, lung cancer, and ovarian cancer.[4] Most BRAF mutations are the result of the point mutation in which valine has been replaced by glutamic acid, at codon 600 (V600E).[2,5] Determining the presence of BRAF mutations plays an important role in the application of targeted chemotherapy, the BRAF inhibitors (e.g. vemurafenib, dabrafenib).[2]

The primary aim of our retrospective study was to determine the impact of targeted therapy on overall survival time (the length of survival since the time of pathohistological diagnosis until end

All patients	N	%	Age at the beginning of disease					
			average	min	max	SD	median	p
Male	19	63.3%	55.6	25	79	13.9	55	0.629
Female	11	36.7%	53.0	29	69	14.9	53	
BRAF +	17	56.7%	49.5	25	74	15.4	51	
Male	10	58.8%	49.8	25	74	15.3	51	0.919
Female	7	41.2%	49.0	29	67	16.7	43	
BRAF -	13	43.3%	61.5	51	79	8.6	63	
Male	9	69.2%	62.1	51	79	8.9	63	0.7
Female	4	30.8%	60.0	52	79	8.6	59	

TABLE 1 Comparison of gender, BRAF status and age at the beginning of disease

of their lives), in a cohort of melanoma patients. The prevalence of BRAF mutations, as well as the pathohistological characteristics (Breslow thickness, initial TNM stage, pathohistological type of melanoma) were analysed.

METHODS

This retrospective study included patients treated for melanoma with metastatic advanced disease at the University Clinical Centre of the Republic of Srpska (UCCRS).

BRAF testing was performed only in patients who had metastatic disease. Detection of BRAF V600 mutation was performed by Real-time polymerase chain reaction (RT-PCR) method, Cobas 4800 System, Cobas BRAF mutation test at the Department of Pathology of UCCRS from 2014 to 2018.

Data on pathohistological and oncological findings were obtained by accessing medical records from the Clinical Informational System. Overall survival (OS) was calculated from the time of pathohistological diagnosis to the time of death. Data were analyzed using descriptive statistics methods (SD, median, and two-sided independent variable Student T-test).

RESULTS

Initially, the study included all patients who were tested for the presence of BRAF mutations between 2014 and 2018, 182 patients in total. All patients who continued their treatment at other institutions in Bosnia and Herzegovina (147 in total) were excluded from the study, because they could not be followed up. UCCRS was a reference center for testing BRAF mutations throughout Bosnia and Herzegovina during that period, because only UCCRS had adequate equipment at the time. Additionally, 5 patients who were alive during our study were excluded from the group.

Patients with primary melanoma of the eye, oral mucosa, and as a metastasis to the brain without known primary localization (N=3.0) had to be excluded when analysing pathohistological characteristics.

Out of 30 patients, 19 (63.3%) were male and 11 (36.7%) were female. Disease was most com-

	N	%	Overall survival (in months)					
			average	min	max	SD	median	p
All patients	30		44.9	2	205	50.0	24.5	0.202
BRAF +	17	56.7%	55.2	4	205	61.8	20.0	
BRAF -	13	43.3%	31.5	2	96	24.5	25.0	

TABLE 2 Review of overall survival of patients in months, compared to BRAF status

Therapy	N	Overall survival (in months)					
		average	min	max	SD	median	p
Vemurafenib*	10	74.3	13	205	72.3	40	0.133
Standard therapy**	7	28.0	4	84	29.7	16	

TABLE 3 Overall survival (in months) in BRAF positive patients related to applied therapy
*Vemurafenib is a type of BRAF targeted therapy, used in our University clinical center.
**Standard therapy for metastatic melanoma in our UCC is cisplatin/dacarbazine (CDDP/DTIC).

monly diagnosed in the sixth decade. Following the RT-PCR Cobas test, 17 (56.7%) patients had a BRAF positive tumor and 13 (43.3%) a BRAF negative tumor (TABLE 1).

Median OS for BRAF positive patients was 20 months (TABLE 2). Most patients who were found to have a BRAF mutation were treated with targeted therapy (vemurafenib), a total of 10 out of 17. The remaining 7 were treated with standard chemotherapy, involving cisplatin and dacarbazine. Median OS in patients treated with vemurafenib was 40 months, compared to median OS of 16 months in patients treated with standard chemotherapy (TABLE 3).

All patients with negative BRAF tumors received standard chemotherapy, with a median OS of 25 months (TABLE 4).

Analysis of the initial pTNM stage, upon the diagnosis of melanoma, showed the following results: pT1a in 1 patient (3.7%), pT1b in 2 patients (7.4%) (pT1 11.1%), pT2a in 1 patient (3.7%), pT2b in 3 patients (11.1%) (pT2 14.8%), pT3b in 6 patients (22.2%) (pT3 22.2%), pT4a in 2 patients (7.4%) and pT4b in 12 patients (44.4%) (pT4 51.85%).

There is no significant difference between BRAF positive and BRAF negative tumors in terms of Breslow thickness (2.3 vs 3.0 mm). Median Breslow thickness, as well as frequency of different pathohistological types of melanoma, are shown in Table 5. Three patients were excluded from this table due to having melanoma of eye, oral mucosis and intial metastasis in brain.

DISCUSSION

Discovery of targeted therapy marked a revolution in oncology.[2] The first targeted melanoma drug was sorafenib (targeted RAF). Due to its reduced selectivity, a new drug was found – vemurafenib, specific for BRAF, and was approved by the Food and Drugs Agency (FDA) in 2011.[2,6]

Observing the latest criteria in the Netherlands, patients with unresectable stage IIIc or IV melanoma are tested for BRAF mutations.[7] BRAF/MEK inhibition is a standard of care for patients with BRAF V600E/K-mutated metastatic melanoma.[8]

Of the 30 patients tested, 56.7% of patients had a V600E mutation, which is consistent with literature, where the frequency of BRAF mutations is about 60%.[2,4] The median age of disease onset in our cohort with BRAF positive tumors is lower, i.e. the disease started earlier (51.0 vs 63.0 years).

The results of our study show that median overall survival for all BRAF positive patients was shorter than for BRAF negative ones (OS 20.0 vs 25.0 months). It should be noted that out of 17 BRAF positive tumors, only 10 patients were treated with vemurafenib for metastatic advanced disease. The health status of the remaining 7 patients did not allow them to receive this therapy.

	N	Overall survival (in months)					
		average	min	max	SD	median	p
BRAF +	7	28.0	4	84	29.7	16	0.782
BRAF -	13	31.5	2	96	24.5	25	

TABLE 4 Overall survival in patients who recieved standard hemiotherapy CDDP/DTIC

	N	%	Breslow thickness (mm)		Type of melanoma		
			median	p	Nodular	Superficial	Acral
Total	27		3.3		23	3	1
					85.2%	11.1%	3.7%
Male	17	63.0%	3.0	0.81	13	3	1
Female	10	37.0%	3.8		10		
BRAF +	16	59.3%	2.3	0.321	13	3	
BRAF -	11	40.7%	3.0		10		1

TABLE 5 Pathohistological characteristics in relation to gender and BRAF status

When comparing patients treated with standard chemotherapy, BRAF positive patients (7 patients, OS 16.0 months) had a shorter OS than BRAF negative patients (OS 25.0 months). Many studies show that overall survival of patients treated with standard chemotherapy is lower for patients with the BRAF V600E (BRAF positive) mutation, than in the BRAF wild type (BRAF negative) patients.[9,10,11,12,13]

In the BRAF positive group, those patients who received vemurafenib in metastatic advanced disease had better OS (40.0 months) than patients treated with standard chemotherapy (cisplatin and decarbazine) (OS 16.0 months), which is in correlation with the literature.[9,14]

Compared to the study done by Heppt et al. (2017) nodular melanoma was also the most common pathohistological type (41.1%), acral lentiginous melanoma was rare, but more frequently occurred in BRAF negative patients. Only 4.2% of patients were detected at the pT4 stage in this study, whereas the majority of our patients were detected at that stage (pT4 51.8%).[9,15]

Although the presence of BRAF mutations plays a major role in the administration of therapy, and thus prolongs patients' OS, it is not an independent prognostic factor for survival.[16]

Two-sided independent variable Student T-test was used in this study, although it is not very reliable in cohort of 30 patients and has a high risk of bias.

Our study showed that vemurafenib, as targeted therapy, showed a better effect on prolonging the life of BRAF positive patients than standard chemotherapy. The use of targeted therapy is of great importance because of its selectivity. Although only patients who had metastatic disease were tested and received treatment in our study, it would be advisable to test all patients diagnosed with melanoma. In our study, in more than half of the patients, the primary tumor was diagnosed at the pT4 stage, indicating a great need for prevention and earlier diagnosis.

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Systematic review and meta-analysis

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At the beginning of the year, all 3rd year medical students have to work on their bachelor thesis. For most of the students, the bachelor thesis is based on a (small) systematic review of existing literature. A systematic review consists of five steps: 1) Search for literature, 2) Selection of studies, 3) Methodological quality assessment of studies, 4) Combining results (meta-analysis), and 5) Assessment of the level of evidence provided by the meta-analysis.

SEARCH FOR LITERATURE

When you search for literature it is important that the research question for the systematic review is clear. When you are searching for randomized controlled trials (RCTs) the question should include the Patient population, the Intervention, the Control condition and the Outcome of interest (PICO). The search is done by some programming in a literature database, such as PUBMED. You should realize that there are more than 15.000 medical journals and probably around a million papers are published each year. This makes the search for literature a hell of a job.

SELECTION OF STUDIES

The problem with the search for literature is that even though the search criteria can be defined in a very accurate way, the number of papers you find is normally very high and therefore a further selection must be performed. This further selection is normally performed by two researchers and is based on the abstracts of the selected papers.

METHODOLOGICAL QUALITY ASSESSMENT

An important aspect of the review is the methodological quality assessment of the studies involved. Please don't believe that papers published in high impact journals are always of high quality. That's not the case. High impact journals such as the Lancet are mostly interested in hot topics and they want to publish papers fast. The problem of fast publishing is that sometimes the quality of the papers is not that good.

COMBINING RESULTS

The combining of the results is the most interesting part of reviewing the literature. It is also the most complicated part. Normally this combining leads to a pooled effect estimate, which can for instance be used by policy makers in order to decide whether or not a new intervention should be implemented. It is also important to have some idea about the differences between the studies that are used to estimate the pooled effect. This 'heterogeneity' is often quantified by I2, which indicates the proportion of total variance explained by the differences between the studies. It is recommended that this I2 should be less than 40%. However, of course, this is an arbitrary cut-off.

IPD META-ANALYSIS

With the increase of open source data bases, the world of meta-analysis is changing. We don't have to rely on published results, but we can use the actual data of different studies to estimate the strength of relationships or treatment effects. This relatively new kind of meta-analysis is known as individual patient data (IPD) meta-analysis. The advantage of IPD meta-analysis is that you can do the analysis by yourself, using state of the art statistical techniques. In traditional meta-analysis you have to use the effects estimated by the involved researchers and sometimes they did the analyses in a slightly different way, or without adjustment for important covariates, etc. When an IPD meta-analysis is performed, these problems are not present.

ASSESSMENT OF LEVEL OF EVIDENCE

After conducting a meta-analysis, it is important to have some idea of the level of scientific evidence provided by the pooled effect estimate. For that purpose the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) scoring system was developed. The GRADE scoring system contains five determinants of quality: 1) limitations of designs, 2) inconsistency in results, 3) indirectness of the results, 4) imprecision of the results and 5) possible publication bias. Based on these five determinants, the level of evidence of each meta-analysis can be judged as high, moderate, low or very low. A comment about publication bias should be made. Publication bias is probably the biggest problem when reviewing the literature. This problem exists because journals are much more willing to publish papers with positive findings than those with negative findings. Although there are methods available (e.g. funnel plots) to evaluate the possibility of publication bias, you can never rule it out. So, in general, you should realize that the pooled effect estimate is an overestimation of the real effect.

Read a paper, but question the statistical analyses? Let us know via AMSj.nl or our Facebook page!

SPOTLIGHT

Surgical closure of high perianal fistulas in Crohn's disease

Elise M. van Praag[1]
1. Department of Surgery, Amsterdam UMC, location AMC, University of Amsterdam

In the column 'Spotlight' we shine a light on students who already published their research in other journals or started their PhD course before graduation.

For this edition we invited Elise van Praag, who is combining a Pre-PhD with clinical rotations.

I am currently more than half-way through my rotations and combining this with a Pre-PhD. This trajectory entails that I currently do research in my 'spare time' and I will finish my PhD with one/one and a half years of fulltime research after I have finished my master.

I first came in contact with research whilst doing the bachelor Psychobiology. I felt then that research was not something I wanted to do fulltime for the rest of my life. It was still too abstract for me, with too much complicated data. When I started medical school one year later, I came to understand more about the importance of research and realised that I missed doing it. I therefore pursued several jobs which involved research, to gain some experience.

When it was time for my bachelor thesis, I carefully thought about what kind of (surgical) research I wanted to do. I always dreamt about becoming a surgeon and during the bachelor I found inflammatory bowel diseases especially interesting. I therefore contacted prof. dr. Bemelman, a colorectal surgeon specialised in minimal invasive surgery in e.g. cancer patients and patients with an inflammatory bowel disease. He suggested researching surgical closure of high perianal fistulas. A perianal fistula is an abnormal tract between the anorectal canal and the perianal skin, which can cause pain, discharge and recurrent abscesses. As you can imagine, this can drastically decrease patients' quality of life. I conducted a systematic review (SR) which focussed on the ligation of the intersphincteric fistula tract (LIFT) procedure (during which a fistula tract is ligated between the anal sphincters in the intersphincteric plane) and the endorectal advancement flap (an alternative in which a flap of mucosal tissue is used to cover the internal opening of the fistula tract).

Whilst doing the SR we found that studies focussing on Crohn's fistulas were scarce, despite the higher incidence and higher risk of incontinence in these patients. We therefore decided to further evaluate these procedures in Crohn's patients. I partially did this in my gap year and continued this research with my master thesis. Afterwards, many more research ideas had emerged. That is when my PhD-trajectory officially started.

Nowadays I greatly enjoy combining research with my rotations. It takes hard work and requires perseverance. I occasionally skip some social activities to be able to manage it all, but I can definitely recommend it. Every researcher experiences setbacks from time to time but in the end hard work will always pay off. Remember that every currently used treatment once had to be researched before it could be implemented. Medicine is always evolving and research is key for that. Please do not feel disheartened when at first some of the terminology or data seem a bit complicated. Things will definitely get better in time!

Articles:

Stellingwerf ME, van Praag EM, Tozer PJ, Bemelman WA, Buskens CJ. Systematic review and meta-analysis of endorectal advancement flap and ligation of the intersphincteric fistula tract for cryptoglandular and Crohn's high perianal fistulas. BJS Open. 2019;3(3):231-41.

van Praag EM, Stellingwerf ME, van der Bilt JDW, Bemelman WA, Gecse KB, Buskens CJ. Ligation of the intersphincteric fistula tract and endorectal advancement flap for high perianal fistulas in Crohn's disease - A retrospective cohort study. J Crohns Colitis. 2019 Nov 7. [Epub ahead of print]

Scrub Typhus in Chile

Sander Kuijpers[1]
1. Department of infectious diseases, Amsterdam UMC, Locaation AMC

Sander Kuijpers recently finished his masters of medicine at the Amsterdam University Medical Center (AUMC) – location AMC. He has an interest in (tropical) infectious diseases and was accepted for a six-month academic internship in infectious diseases partly out on the field in Chilean Patagonia and partly at the Universidad Católica de Santiago, a teaching hospital in Santiago de Chile.

THE INTERNSHIP

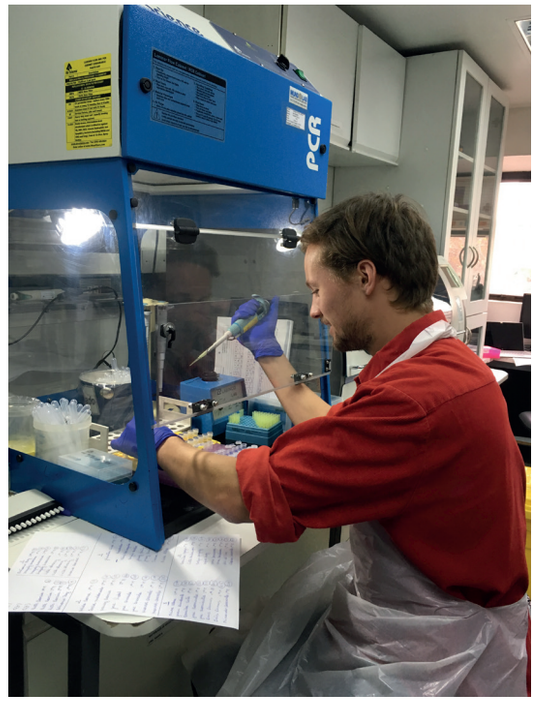
In my academic internship I performed a study in a semi-rural hospital in Ancud, Chiloé. On this island in Chilean Patagonia 40 cases of Scrub Typhus (ST), an infectious disease caused by the rickettsial bacterium Orientia tsutsugamushi, have been diagnosed to date. This is interesting, because ST was thought to occur only in South East Asia. Diagnosis is difficult, because often fever is the only presenting symptom.

I looked for (a)typical cases of ST among patients with fever that visited the emergency

ward and took serum samples for the comparison of several diagnostic tools that are currently in use in South East Asia. After three months I moved to Santiago and worked on the analysis of the constructed database and the diagnostic interpretation of the samples. We showed that, when using the Asian test kits, diagnosis was more difficult because diagnostic accuracy was lower and serology cut-offs had to be adapted. Antigenic difference of the Chilean strain could partly explain this diagnostic problem. In the future culture of this organism should be performed to develop our own antigenic serology tests.

APPLICATION

The initiator and supervisor of this project was professor Martin Grobusch from the AUMC tropical center. He put me in contact with his colleagues of the department of infectious diseases on the other side of the world. Financial support was provided by the 'Amsterdams Universiteitsfonds', available for all Amsterdam students going abroad, and the local FONDECYT fund. Approval follows the same procedures as for internships performed in the Netherlands and is managed from within the University of Amsterdam.



RESEARCH ABROAD

A few differences between research in Chile and the Netherlands exist. Funding for research projects is not as widespread as in the Netherlands, and staff dedicated only to research is very rare. Doctors always have to work in an outpatient clinic to maintain a salary and development of research is not priority. My help consequently was very welcome and from the first day I felt accepted in the team. I hold my supervising professors, Katia Abarca and Thomas Weitzel, in high regard. They

devoted many of their personal hours to increasing the awareness of this potentially deadly infectious disease in Chile.

My fantastic time here certainly paid off. In November we were invited to the Asian Pacific Rickettsia Conference in Thailand where I presented two of our research projects. Doing research abroad is challenging. Much more discipline and independence is needed to stick to the project, especially in rural hospitals far away from daily supervisors. An open mind and willful attitude also help to connect with local cultures. The existing language barrier made the inclusion of patients and first contact with the direct supervisors difficult, but it also forced rapid learning and full immersion in the foreign culture. If you accept the risks of doing research abroad and have a flexible attitude, you just might learn a lot more than merely research skills.

Modern Day Treatment of Heel Bone Fractures: the Sinus Tarsi Approach

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There has been an increase in patients with a displaced intra-articular calcaneal (heel bone) fracture (DIACF) that are treated via the minimal invasive sinus tarsi approach (STA).[1] The treatment of DIACFs has been extensively debated and has changed over time.[2] In the 20th century treatment options included no reduction or closed reduction but during the last decade open reduction and internal fixation with or without primary arthrodesis via the extended lateral approach (ELA) became the treatment of choice.[2,3] However, wound complications occur in 20.0% of patients.[3] The alternative minimally invasive option is the STA in which an incision is made from the tip of the fibula to the base of the fourth metatarsal.[4] Due to this small incision with less soft tissue damage, it has been hypothesized that patients treated via the STA have a lower postoperative infection rate.[4] As shown by Nosewicz et al. the STA is associated with less postoperative wound complications compared to ELA in patients with a DIACF (4.9% versus 20.4%, respectively).[4] Moreover, similar functional results and anatomic reduction can be obtained although this surgical technique is more challenging to master.[4] In conclusion, the outcomes are promising and it is believed that the treatment of DIACFs will shift further towards the STA.

Goslings JC, Schepers T. A systematic review and meta-analysis of the sinus tarsi and extended lateral approach in the operative treatment of displaced intra-articular calcaneal fractures. Foot Ankle Surg. August 2018. doi:10.1016/j.fas.2018.08.006

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A young male with general malaise

S. van Beem[1] and M. Maas[2]
1. Faculty of medicine, Amsterdam UMC Location VUmc, VU University
2. Department of Radiology, Amsterdam UMC Location AMC, University of Amsterdam
Acknowledgements dr. A. van Randen (cardioradiologist AMC)

CASE

A 25-year old male presented at the ER with acute onset general malaise and fatigue. His medical history shows stable ulcerative colitis, treated with Salofalk 1000 mg 3 dd (mesalazine) and Minoxidil foam. An MRI of his chest was performed.

QUESTION 1

What do you see?

A. Increased mid myocardial enhancement on the lateral side
B. Decreased left ventricular myocardial enhancement
C. Aortic valve vegetation
D. Polo mint sign

Hint: in what kind of patient would you expect each finding?

QUESTION 2

What is your diagnosis?

A. Myocardial Infarction
B. Endocarditis
C. Pericarditis
D. Embolism

Hint: which part of the heart seems affected in the MRI?

QUESTION 3

What would most likely be the cause in this patient?

A. Auto-immunity
B. Trauma
C. Idiopathic
D. Virus
E. Medication

Hint: take the medical history of the patient into consideration!

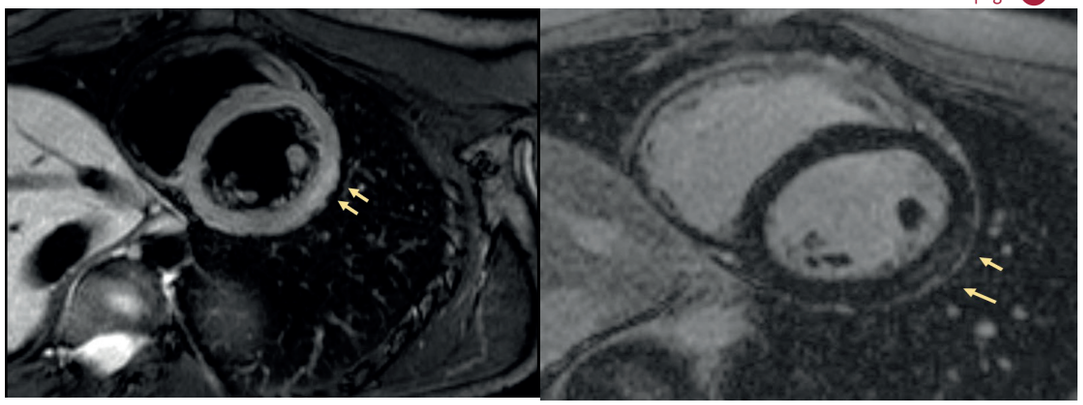
QUESTION 4

What are other modalities to diagnose this condition (multiple answers possible)?

A. Transthoracic echocardiography (TTE)
B. ECG
C. Auscultation
D. X-ray
E. Blood test

Hint: what would you expect to find with each test?

Answer on page 23



Answers 'Headache and blurry vision'

S. Amlal and M.C. Brouwer

Correct answers: 1A, 2A 3D.

EXPLANATION

QUESTION 1

To describe and get more insight on normal and abnormal structures on MRI, the shade of grey of tissues and fluid are referred to in terms of 'intensity'. Hyper- and hypointense signals are respectively visible as white and black shades on MRI. In T1-weighted sequences, grey matter appears as an intermediate (grey) signal and white matter as a hyperintense (white) signal. Reverse signals can be seen for T2. T1-weighted sequences are the preferred images for evaluation of the cerebral anatomy, because they most closely represent the structures in reality. Intravenous contrast agents show disruption of the blood-brain barrier as an increased signal on T1 and this is commonly found in tumors or areas of inflammation. When diffusion weighted sequences (e.g. DWI, ADC) are described, the terms 'restricted' or 'facilitated' diffusion are also used, which denote to what extent water molecules can move within tissues. These sequences are useful in the context of acute pathology such as tumors, ischemia and edema. DWI shows areas with restricted diffusion as a hyperintense signal, while apparent diffusion coefficient (ADC) maps denote it as a decreased signal.

T1 with contrast, a hypointense lesion in the left occipital lobe is seen with ring shaped contrast enhancement of the lesion surrounded by a hypointense area consistent with cerebral edema.

T2, the lesion core is hyperintense, indicating the core has a high water content. Edema surrounding the ring-enhancing lesion appears hyperintense on this sequence. The ring of the lesion is isointense.

DWI, the core of the lesion has a hyperintense signal denoting restricted diffusion

ADC, the core of the lesion has a hypointense signal denoting restricted diffusion

QUESTION 2

A (Cerebral abscess) Correct, the combination of severe headache, fever, flu-like symptoms and multiple dental surgeries in the medical history is highly suggestive of a cerebral abscess. Cerebral abscesses develop from a throat-nose-ear or hematogenic (often originating from infections in the lungs or from congenital heart disease) focus. Symptoms are non-specific to such an extent that even signs and symptoms of (systemic) infection can be completely absent. 70-90% of patients complain of a progressive severe headache that is sometimes accompanied by nausea and vomiting as a result of increased intracranial pressure. An impaired immune system (e.g. autoimmune diseases, organ transplantations, corticosteroid use, HIV and hematologic malignancies) and head surgery in the medical history are important risk factors. The blood leukocyte count is raised in only 50% of the cases and in 75-90% there is also an increased ESR. The diagnosis is ultimately made by CT or MRI on which a ring-like enhanced lesion showing central diffusion restriction is visible.

B (High-grade glioma) Incorrect, metastases or high-grade gliomas such as glioblastoma should be in the differential diagnosis, because these lesions also typically appear as ring-enhancing lesions on neuroimaging. However, tumors often have a more irregular inner wall and show central facilitated diffusion.

C/D (Subacute hemorrhage/Subacute infarction) Incorrect, hemorrhagic and ischemic strokes typically present with a more rapid onset of neurological symptoms, which worsen within hours depending on the size of the affected brain area. Intracerebral hemorrhages are visible as a hyperintense (T1) or hypointense (T2) lesion without a surrounding reverse rim-signal as is seen in context of abscesses or cystic brain malignancies. In case of infarction, the ischemic parenchyma is also visible as an increased DWI and reduced ADC signal, but the affected site often appears normal on the other MRI sequences. For both diagnoses, non-contrast CT is the preferred radiological diagnostic tool.

QUESTION 3

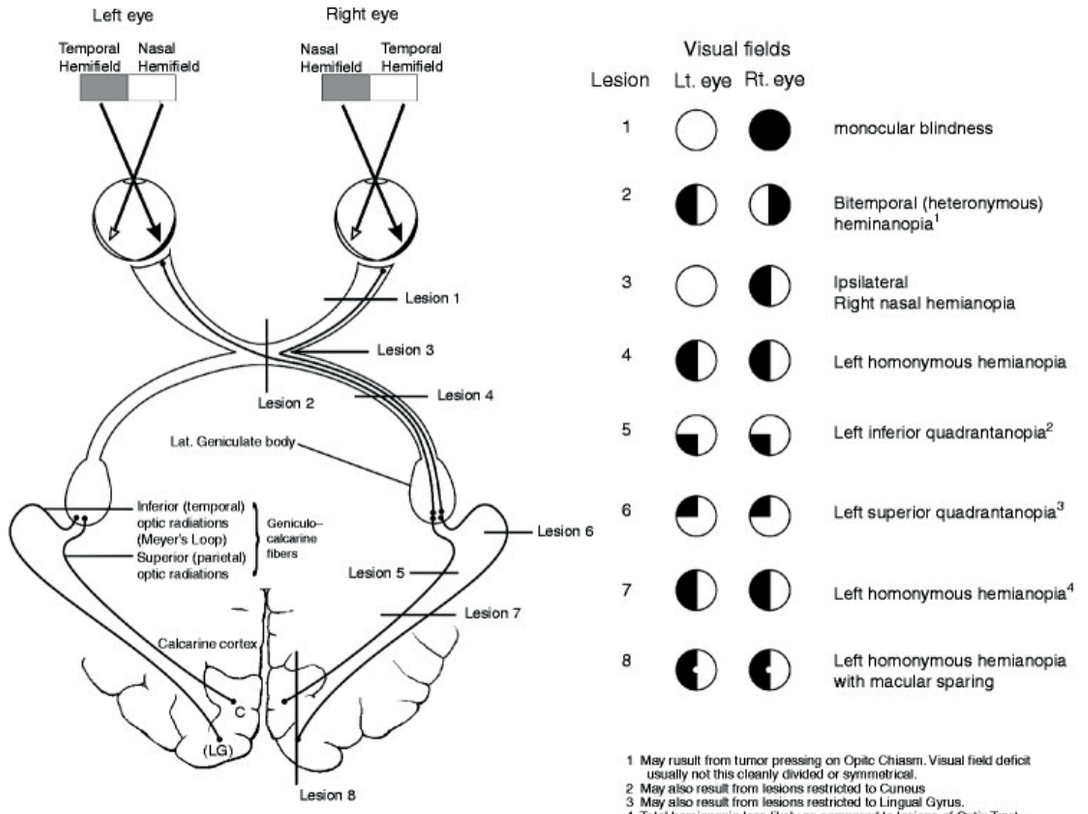
A (Bitemporal hemianopsia) Incorrect, this medical term is used for a visual field abnormality in which the patient is suffering from blindness of the temporal parts of the view (i.e. left versus right half of the visual field). It is associated with lesions of or close to the optic chiasm (e.g. pituitary gland abnormalities), where the optic nerves cross and proceed to the lateral geniculate nuclei. A synonym for this term is 'heteronymous hemianopsia'.

B (Monocular vision loss) Incorrect, in this case, there is an ocular lesion or abnormality anterior to the optic chiasm, which causes entire blindness of one eye. In this

case, there is an ocular lesion or abnormality anterior to the optic chiasm, which causes entire blindness of one eye.

C (Heteronymous hemianopsia) Incorrect, this is a synonym of the term 'bitemporal hemianopsia'. See explanation of answer A.

D (Homonymous hemianopsia) Correct, the lesion visible on the MRI is located in the primary visual cortex of the left occipital lobe which has led to blindness of the right visual field half of both eyes. The patient may retain the macular vision in the central part of the right visual field ('macular sparring').



Answers 'A young male with general malaise'

S. van Beem and M. Maas

Correct answers: 1A, 2C, 3E, 4ABCD

EXPLANATION

The MRI shows an increased mid myocardial enhancement on the lateral side, which normally should be a homogenous low signal. This indicates active pericarditis.

Pericarditis is characterized by swelling and irritation of the pericardium. Pericarditis can be either acute (<3 weeks) or chronic and patients usually present with a sharp chest pain as a result of friction between the irritated layers of the pericardium. Other symptoms include general malaise, fatigue, shortness of breath and a cough.

There are several underlying causes of pericarditis, but in developed countries 80% of the cases are either idiopathic or postviral.[1] Other causes include trauma, systematic inflammatory disorders such as SLE or certain types of medication. Although recurrent pericarditis can be a rare extra-intestinal manifestation of ulcerative colitis[2], in our patient the pericarditis was most likely attributable to the use of Salofalk (risk of pericarditis= 0.01-0.1%) and Minoxidil (risk of pericarditis= 10%).

Pericarditis can be suspected upon auscultation, where a pericardial friction rub can be heard. Laboratory findings in pericarditis are often linked to inflammation, such as increased white blood cell counts and CRP, but are insufficient to diagnose pericarditis. ECG often shows new widespread ST elevation or PR depression. TTE (the modality of choice) might show pericardial effusion. Chest X-ray is usually normal in acute pericarditis but might show an enlarged cardiac silhouette.[3]

CT and MRI of the heart are increasingly used, with around 40 CTs and MRIs of the heart performed weekly in the Amsterdam UMC- location AMC alone. In the diagnosis of pericarditis, MRI and CT are specifically useful in patients presenting with atypical symptoms (think of our patient presenting with general malaise, but no remarkable chest pain), progression towards constrictive pericarditis or in patients with longstanding pericarditis. Both CT and MRI can detect small pericardial effusion which would have been missed with TTE.[4]

Treatment of pericarditis depends on the cause and severity, where mild cases are often self-limiting and can be treated with NSAID and colchicine. Other treatment options include glucocorticoids. The main complications of pericarditis are constrictive pericarditis and cardiac tamponade, the latter requiring pericardiocentesis.[5] Our patient was treated by the discontinuation of Minoxidil.

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Colophon

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