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Editorial office
Erasmus MC, University Medical Center Rotterdam
Department of Internal Medicine 's-Gravendijkwal 230
3015 CE Rotterdam
The Netherlands
Tel.: +31 (0)10-703 59 54
Fax: +31 (0)10-703 32 68
E-mail: p.l.a.vandaele@erasmusmc.nl
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EDITORIAL

Personalised anticoagulation therapy: towards a multidisciplinary approach in integrated antithrombotic care

M.B. Mulder 10, N.G.M. Hunfeld 1,2

Departments of 1Hospital Pharmacy, 2Intensive Care, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands. *Corresponding author: m.b.mulder@erasmusmc.nl

For decades, vitamin K antagonists (VKAs) were the cornerstone for the prevention and treatment of venous and arterial thrombosis. VKAs show a high variability in patient response, primarily genetic polymorphisms in CYP2C9 and VKORC1.1 By determining a pharmacogenetic profile, anticoagulation therapy could be initiated based on a personalised advice. Currently, direct oral anticoagulants (DOACs) and low-molecular weight heparins (LMWHs) are frequently used. LMWHs in therapeutic doses are mainly used for bridging during perioperative interruption of VKA treatment, initial treatment of venous thrombo-embolism (VTE), and cancer-associated VTE. Current guidelines recommend monitoring anti-Xa levels in patients with renal insufficiency, pregnancy, and obesity.2 However, is it feasible in clinical practice to monitor every patient and obtain reliable results?

In the current issue of the journal, van Bergen et al. assessed compliance of adequate monitoring anti-Xa levels in their hospital. They show that monitoring anti-Xa levels is challenging and difficult to implement in a clinical setting. Furthermore, based on a study by Smit et al., lowering the LMWH dose in accordance with current guidelines results in subtherapeutic anti-Xa levels after the first measurement in many patients.3 Therefore, introducing and implementing good protocols for monitoring LMWHs will be needed in order to optimise and personalise LMWH therapy.

The Dutch guideline on integrated antithrombotic care (‘Landelijke Standaard Ketenzorg Antistolling’) provides a standard for anticoagulant therapy. Recently, Dreijer et al. studied the effect of a multidisciplinary antithrombotic team on bleeding complications and thrombotic events and adherence to anticoagulant guidelines among prescribing physicians.4 5 They show that introduction of a multidisciplinary antithrombotic team leads to a significantly higher overall adherence to anticoagulant guidelines among prescribing physicians, primarily based on the improvement of LMWH dosing. Two recommendations in the thesis of Dreijer for clinical practice are:6 a multidisciplinary antithrombotic team focusing on education, medication reviews by hospital pharmacists, drafting of local anticoagulant therapy guidelines, patient counselling and medication reconciliation at admission and discharge, which increases the effect and safety of antithrombotic therapy; and introducing a clinical rule, based on one nationally adapted guideline, combining the renal function and bodyweight of the hospitalised patient with the prescribed LMWH could be useful to further improve adherence and implement adequate anti-Xa level monitoring.

We hope we inspired you to take up the challenge and start implementing a multidisciplinary antithrombotic team in your hospital.

REFERENCES

Diagnostic and (new) therapeutic options for resistant hypertension: a short review

L. Feyz¹, L. Peeters², J. Daemen¹, J. Versmissen³*

Departments of ¹Cardiology, ²Internal Medicine, Erasmus Medical Centre, University Medical Centre, Rotterdam, the Netherlands. ³Corresponding author: j.versmissen@erasmusmc.nl

ABSTRACT

Hypertension is a major risk factor for ischaemic heart disease and stroke. Despite the availability of numerous pharmacological treatment options, blood pressure (BP) targets are often not achieved. The inability to reach BP levels below 140/90 mmHg despite the use of three or more antihypertensive drugs is defined as resistant hypertension (RH). The etiology for RH is multifactorial. First, BP should be appropriately measured. In order to improve BP control, lifestyle modification should be recommended, adherence should be carefully assessed to exclude pseudo-resistance, and efforts should be made to exclude secondary causes of hypertension before initiating new drugs or considering device-based treatment strategies. This short review will highlight several aspects of RH management along with a focus on several new treatment options.

KEYWORDS

Adherence, device-based therapy, hypertension, resistant hypertension

CASE PRESENTATION TO INTRODUCE THE TOPIC

A 55-year-old female with a history of Graves’ disease and thyroidectomy was referred due to severe hypertension from which she suffered for over 20 years. The patient reported that several antihypertensive drugs were replaced due to side effects, including perindopril, which was discontinued due to a dry cough and doxazosin, which was stopped due to palpitations. Despite a regimen of valsartan 320 mg once a day (qd), hydrochlorothiazide 25 mg qd, amlodipine 10 mg qd and metoprolol 100 mg qd, her blood pressure (BP) remained uncontrolled. She reported to be fully adherent to all medications. In addition to antihypertensive drugs, she was taking levothyroxine 100 microgram qd. Most of the time when she was late from work, she ordered ready-meals (3-4 times a week). Physical and laboratory examination including 24 hr urine sodium measurement and thyroid function tests revealed, in addition to a severely elevated BP (200/120 mmHg, heart rate 75 beats/min) and a high-salt intake of 170 mmol/24 hrs, no further abnormal findings. Additional workup showed no relevant secondary causes of hypertension. Twenty-four-hour ambulatory blood pressure monitoring (24h ABPM) confirmed true resistant hypertension with mean daytime BP 145/98 mmHg. Her physician proposed to intensify her antihypertensive drug regimen and offered her dietary support to reduce salt intake. However, the patient was curious about a new technology that she had read about on Facebook, something with heat and nerves that could result in a better blood pressure control: would she be a candidate for this technique?

DEFINITIONS

With the recent changes in the European and American hypertension guidelines, BP targets are lower than ever.1,2 However, the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) and the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guidelines vary in the recommendations regarding when treatment should be initiated. The ESC/ESH guidelines recommend initiation of treatment at an office systolic BP of ≥ 140 mmHg and/or a diastolic BP ≥ 90 mmHg, with 24h ABPM values, in general, being lower than the office BP values (diagnostic threshold for hypertension is a mean daytime ABPM ≥ 135/85 mmHg). The ACC/AHA guidelines advocate an even lower threshold for commencing treatment (office BP ≥ 130/80 mmHg, daytime 24h ABPM >130/80mmHg).3
These thresholds were based on multiple clinical trials and meta-analyses, showing the beneficial effects of BP-lowering therapy on cardiovascular events.\(^3\)\(^-\)\(^7\) Regardless of the final target value, Ettehad et al. showed that every 10 mmHg reduction in systolic BP significantly reduced the risk for all major cardiovascular events by 20\% and led to a significant 13\% reduction in all-cause mortality.\(^1\)

BP that remains uncontrolled (> 140/90 mmHg) despite the prescription of three antihypertensive drugs (with at least one diuretic) is considered ‘resistant hypertension’ (RH).\(^8\) The RH definition was initially established to identify a high-risk patient population that would benefit from more specialised care and specific diagnostic testing.\(^9\) However, the definition remains rather nonspecific and could include patients with either true or pseudo-RH. Several factors play a role in persistent uncontrolled hypertension, and therefore a stepwise approach is recommended.

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**Figure 1. Stepwise approach in patients with RH**

*Based on the recent results of the RADIANCE-HTN SOLO and SPYRAL OFF-MED trial, RDN may be considered earlier than mentioned in the flowchart (e.g., patients with a high-risk cardiovascular profile).*

BP = blood pressure; DOT = directly observed therapy; GP = general practitioner; OSAS = obstructive sleep apnoea syndrome; RH = resistant hypertension; TDM = therapeutic drug monitoring.
**STEPWISE APPROACH**

**General clinical characteristics**

The American Heart Association emphasizes that RH is a multifactorial problem; individual patient characteristics include lifestyle factors, potential secondary causes of hypertension including drug-related causes, and potential pseudo-resistance should be assessed. Several patient characteristics such as older age, obesity, excessive sodium intake, diabetes, black race, female gender, high baseline systolic BP, and target organ damage (chronic kidney disease and left ventricular hypertrophy) proved to be strong predictors for uncontrolled BP. Lifestyle factors such as excessive sodium intake and heavy alcohol intake should be discussed and discouraged. Pimenta et al. studied the effect of dietary salt restriction on office and 24h ABPM in patients with RH, and demonstrated that low versus high-salt diet decreased both office BP (systolic and diastolic decrease of 2.7/9.1 mmHg, respectively) and 24h ABPM (20.7/9.6 mmHg). Additionally, the degree of BP reduction induced by salt restriction in the cohort with RH was larger than reductions observed in the normotensive cohort. These results demonstrate the importance of salt restriction in patients with RH.

A recently published randomised trial showed the effect of lifestyle change and weight management in football fans, in which the lifestyle programme helped to improve weight, waist circumference, and vitality, and significantly reduced diastolic BP at 12 months (mean difference between intervention and control group -1.2 mmHg (95% CI: -2.1 to -0.4, p = 0.004). Pharmacological agents that could increase BP such as the use of nonsteroidal anti-inflammatory agents, oral contraceptives, and sympathomimetic agents (cocaine), should be dissuaded. Furthermore, care should be taken in performing accurate BP measurements and general clues that could reveal secondary causes of hypertension should be identified during outpatient clinic follow-up. Additionally, non-adherence to prescribed antihypertensive drugs should be assessed.

**Appropriate BP measurement**

Inaccurate BP measurements proved to be a frequent cause of pseudo-resistance. Automatic office BP measurement is recommended and BP should be measured in both arms during the first visit. As a rule of thumb, the health care provider should measure BP three times with intervals of at least one minute. The average of the last two measurements in the arm with the highest BP value should be used as a reference at follow-up. In the most optimal setting, BP should be measured unattended. Frequent mistakes comprise measuring BP before the patient could sit quietly for a couple of minutes and using small BP cuffs, which will result in falsely high BP measurements.

The gold standard, to rule out white coat and masked hypertension, is a 24h ABPM, which should be performed in all patients with suspected RH. Furthermore, home BP assessment proved to be a better predictor for cardiovascular morbidity than office BP. When home BP is combined with physician counselling, the adherence to antihypertensive drugs could improve, resulting in better BP control. Home BP measurement is recommended when the patient is able to measure his/her BP by an automatic BP monitor.

**Exclude secondary causes for hypertension**

Secondary causes of hypertension can be found in up to 10% of cases. True RH should be the trigger towards more extensive workup. Attention should be paid to symptoms of snoring, daytime sleepiness, and morning headache, especially in overweight and obese patients in order to detect obstructive sleep apnoea which proved to be twice as common in RH compared to non-RH patients, with incidences reported to be more than 30%. Furthermore, other relatively common causes should be excluded based on clinical and laboratory findings such as renal parenchymal disease (e.g., especially in patients with diabetes or smokers; generalised atherosclerosis; and previous renal failure, for which, screening should be done with kidney ultrasound) and primary aldosteronism (6-23% of RH cases; clinical findings include observed muscle weakness; complaints of fatigue; constipation; polyuria and polydipsia) (figure 1). Finally, renal artery stenosis is a known secondary cause of RH present in 2-20% of RH cases and is either caused by atherosclerosis or fibromuscular dysplasia. Occurrence of flush pulmonary oedema might unravel bilateral renal artery stenosis. The importance of treatment, and in particular renal artery stenting or balloon dilatation, remains debated, but should be considered, especially in patients with rapidly decreasing kidney function or in patients with only one functional kidney.

More uncommon causes to be ruled out include Cushing’s syndrome (<1%), as well as hypo- as hyperthyroidism, coarctation of the aorta (<1%) and phaeochromocytoma (<1%). Of note, while helpful in lowering BP and improving patient prognosis, treatment of secondary causes does not always lead to normalisation of BP and pharmacotherapy remains necessary.

**Exclude non-adherence**

One of the main causes of pseudo-RH is non-adherence, with a reported prevalence ranging from 23-66%. Non-adherence can mean that a patient is non-adherent to all drugs (full non-adherence) or to a limited number of drugs (partial non-adherence). As a matter of fact,
Direct methods, however, are a promising treatment option to non-adherence to antihypertensive drugs, as an underlying cause is the most difficult cause to treat for RH. A crucial step in the management of hypertension and especially in patients with RH, is the assessment of adherence to antihypertensive drugs. Assessing adherence has been recognised as the first step in improving non-adherence and clinical outcome. Scotti et al. showed that an enhancement of adherence from 52% to 60-80% led to a reduction in cardiovascular events from 85 to 83, and 77 events every 10,000 person-year, respectively. Clinicians in general tend to overestimate adherence rate. Several methods are available to assess adherence such as pill counts, patient self-reports, directly-observed therapy, and measurement of drug or metabolite levels. Direct methods (such as directly-observed therapy, electronic monitoring, and therapeutic drug monitoring (TDM)) are more accurate and reliable than indirect methods (such as questionnaires or pill count). Direct methods, however, are more expensive and more labour-intensive. In more complex cases, a combination of TDM and directly-observed therapy might provide a better understanding and facilitate further counselling on drug adherence. Once non-adherence has been objectified, efforts should be made to find the underlying cause to help the patient in finding a solution. In a small pilot study, it appeared that using TDM to identify non-adherence, followed by counselling, led to improvement of adherence and BP regulation. Currently, the effect of TDM combined with counselling based on finding the underlying cause for non-adherence to improve BP regulation in pseudo-RH is being assessed in the Resistant Hypertension: Measure to Reach Targets (RHYME-RCT) (trialregister.nl; NTR6914, RHYME-RCT).

**TREATMENT OPTIONS**

**Pharmacotherapy**

The 2018 ESC/ESH guideline recommends the initiation of pharmacological treatment within the five major antihypertensive classes: angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor inhibitors (ARBs), calcium channel blockers (CCBs), diuretics, or beta-blockers, in which an overview per drug class and possible side effects can be found. When focusing on patients with RH, without finding a secondary cause and after confirming adherence to the prescribed antihypertensive drugs, BP targets can often still be achieved by optimising antihypertensive drug regimens (including a fixed-dose combination therapy). As a next step to an ACE inhibitor or an ARB (a CCB and a diuretic), the addition of spironolactone has shown to be effective in lowering BP. In the PATHWAY-2 study (Prevention and Treatment of Hypertension with Algorithm-based therapy-2), the BP lowering effect of spironolactone (25-50 mg) was greater than doxazosin and bisoprolol. New antihypertensive drugs, which are being studied, primarily target the renin-angiotensin-aldosterone system (RAAS), such as aldosterone synthase inhibitors or non-steroidal mineralocorticoid receptor blockers, with the aim to reduce the anti-androgenic side effects. Although vaccines targeting RAAS components were considered treatment options to avoid adherence issues, pharmacokinetic and pharmacodynamics issues hampered further development. A promising treatment option to date, is the combination of angiotensin II receptor blockade and neprilysin inhibitor (ARNI), currently registered for heart failure. ARNIs showed significantly greater reductions in BP as compared with an ARB alone and have been proven safe and well-tolerated.

**Device-based therapy**

Despite currently available interventions targeting lifestyle and pharmacotherapy including drug adherence, it is often not possible to reach the target BP. A recent study by Patel et al. reported that when causes for pseudo-resistance including non-adherence were excluded, 15% of patients with RH may be eligible for device-based therapies for hypertension. Moreover, recent studies showed that patients would prefer device-based therapy that may diminish the need for more antihypertensive drugs. Hutchins et al. showed that approximately one out of three respondents would be willing to trade two years of their life to avoid taking drugs. Additionally, respondents were willing to pay an average of $1,445 to avoid daily medication. At present, several device-based therapies have been studied to control BP as an alternative or add-on therapy in patients with RH, by primarily targeting the autonomic nervous system.

**Renal denervation**

The most studied device-based therapy to date is renal sympathetic denervation (RDN). The percutaneous treatment targets renal sympathetic nerves at the renal artery level and demonstrated reduction of sympathetic overactivity. Although several promising trials have been published, the treatment faced a significant decline in enthusiasm following the neutral results of the first sham-controlled RDN trial, the Symplicity HTN-3 trial (Renal Denervation in Patients With Uncontrolled Hypertension) in 2014. Dissecting the trial design identified several factors that could potentially have led to the failure of the trial of meeting its primary endpoint. As such, inadequate screening, frequent changes in antihypertensive regimens and the use of a first-generation RDN device along with a lack of operator experience were suggested to be responsible. Subsequently, three proof-of-principle studies with more advanced trial designs, proved the overall efficacy and safety of the
technique.\textsuperscript{54-57} Both RDN techniques used in these studies seem efficacious in achieving a significant drop in blood pressure of approximately 6 mmHg as compared to a sham comparator arm at 2-3 months. The body of evidence supporting the efficacy of the treatment in patients with RH is steadily increasing. Given the positive data available thus far, referring patients with true RH to specialised centres participating in dedicated RDN trials should be strongly encouraged.

Several studies on BP efficacy and safety of renal sympathetic denervation, with strict entry criteria, are ongoing (RADIANCE II Pivotal; TRIO; NCT03164260; NCT02649426; REQUIRE study NCT02918305).

**Barostim Neo system**

Carotid baroreflex activation therapy is a relatively new surgical implantable device which stimulates the carotid baroreceptors and therefore down-regulates the sympathetic outflow with an increase in parasympathetic tone.\textsuperscript{58,59} The first sham-controlled studies in patients receiving bilateral implants showed significant BP reduction with a clear on/off phenomenon.\textsuperscript{58,60} A recently published study on the safety profile and efficacy of a second generation of the device, the Barostim Neo, showed that side effects such as syncope, hypertensive crisis, and arrhythmias occurred in 28% of patients. A significant BP drop was seen at six months in patients treated with Barostim Neo (from a mean of 169 ± 27 to 148 ± 29 mmHg, p < 0.001) and one year (a further decrease to 145 ± 24 mmHg as compared with baseline, p < 0.001) follow-up with a significant decrease in prescribed antihypertensive drugs.\textsuperscript{19} However, due to current lack of randomised controlled trials, the side effects, the high costs, and the need for frequent battery replacement, there was a quest for alternative methods to stimulate the baroreflex and lower BP.\textsuperscript{58,60}

**Mobius HD system**

Carotid baroreceptor amplification therapy, the Mobius HD system, is an endovascular carotid implant. Its mechanism of action is based on passive activation of the baroreceptor by irreversibly changing the carotid sinus shape, resulting in pulsatile wall stretch and a linear increase in firing rate when BP increases.\textsuperscript{61} The latter phenomenon suppresses the sympathetic outflow and consequently decreases BP. The CALM-FIM study (Controlling and Lowering Blood Pressure with the MObiusHD) showed that the Mobius HD device significantly reduced BP (by 21/12 mmHg at 6 months, p < 0.001), however this was a non-randomised, open-label study.\textsuperscript{62} Two patients developed neurological symptoms after implantation. CALM-2 study is now enrolling to further study the efficacy and safety (ClinicalTrials.gov NCT03179800).

**Other non-pharmacological interventions**

A number of non-pharmacological therapies are in the pipeline at different stages of development, such as the alcohol-mediated perivascular renal denervation with the Peregrine SystemTM (Ablative Solutions)\textsuperscript{64} and the ROX AV coupler (ROX Medical) which creates an arteriovenous (AV) anastomosis between the external iliac artery and vein to reduce vascular resistance and the effective arterial volume, that could immediately result in significant reductions of BP.\textsuperscript{65} Several studies are ongoing to evaluate their safety and efficacy further (Peregrine system, TARGET BP OFF-MED trial, NCT03507773; ROX coupler (CONTROL HTN-2 NCT02893386).

In general, based on the recent 2018 ESC/ESH guidelines, device-based therapy for hypertension is not recommended for the routine treatment of hypertension, unless performed within the context of a clinical (randomised) trial. The results of current ongoing larger clinical trials will provide more details on the safety and efficacy of the technology.\textsuperscript{66}

**Back to the case**

Despite a substantial decrease in urine sodium excretion from 170 to 130 mmol/24h, BP remained uncontrolled. Further work-up of our patient included drug adherence testing using TDM in which we measured the drug levels by venous sampling. After confirming full adherence, spironolactone was added to her drug regimen resulting in daytime average 24h ABPM of 141/90 mmHg (mean office BP 165/100 mmHg). Due to a lack of response to the therapy above, the patient was enrolled in a double-blind, randomised controlled trial to assess the efficacy and safety of RDN in patients with RH.

**CONCLUSION**

The management of RH should contain advise on lifestyle modifications including the reduction of sodium intake, and accurate BP measurement, preferably by 24h ABPM, to rule out pseudo-RH. Additionally, assessment for secondary causes of hypertension should be considered and non-adherence to prescribed antihypertensive drugs should be ruled out. To note, adding a mineralocorticoid receptor blocker to the existing antihypertensive regimen could lead to an additional BP drop, also in essential hypertension. New drug- and device-based treatment options have been studied extensively over the past years, with promising results in the general hypertensive population. More evidence is warranted in order to determine the clinical relevance and cost-effectiveness of device-based therapies as compared with existing pharmacological treatment options.
DISCLOSURES

Joost Daemen received institutional research support from Medtronic, PulseCath, Abbott Vascular, Acist Medical, and Pie Medical, as well as consultancy and lecture fees from Acist Medical, Medtronic, PulseCath, and ReCor Medical. For the remaining authors no conflicts of interest were declared.

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The diagnosis of male breast cancer

M.N. Nofal, A.J. Yousef*

General Surgery and Anaesthesia Department, College of Medicine, Mutah University, Jordan. *Corresponding author: alijad30@hotmail.com

ABSTRACT

Background: To review the procedural diagnosis of male breast cancer.

Methods: Medline and Google Scholar searches using the terms (male breast cancer) and (diagnosis); and (triple assessment).

Results: Most of the search-specific items are incorporated in more comprehensive reviews about male breast cancer in general. Relevant data was extracted in accordance with the aim of this review.

Results: Most of the diagnosed cases are advanced stage ductal invasive carcinomas, express hormone receptors in the great majority, and are less likely to over-express HER2-neu. They present usually as a painless retroareolar mass that requires triple assessment. The diagnosis needs a high index of suspicion primarily due to the unawareness of such a cancer in males.

KEY WORDS

Breast biopsy, breast ultrasound, clinical assessment, diagnosis, male breast cancer, mammography, triple assessment

INTRODUCTION

Male breast cancer is a rare malignancy comprising less than 1% of all male cancers and is not completely understood because most of the available data is obtained from single institution studies with no statistical significance.1 Traditionally, male breast cancer was thought to be similar to post-menopausal female breast cancer, but emerging evidence suggests that male breast cancer may be different.2 From the clinical and biological points of view, male and female breast cancers differ primarily in the frequency of their histological types and in the expression of hormone receptors (oestrogen receptor (ER) and progesterone receptor (PR)) and the human epidermal growth factor receptor 2 (HER2).3

DISCUSSION

The diagnosis of male breast cancer can be made in most cases by triple assessment: clinical assessment, radiologic assessment (mammography and ultrasound examination), and tissue biopsy (fine-needle aspiration cytology or core biopsy), exactly as in female breast cancer.

Clinical assessment

The most common symptom of breast cancer is a painless retroareolar mass which is present alone or with other symptoms in 75% of all cases. The mass is found more frequently on the left more than on the right,4 and pain is present with the mass in 5% of all patients.5 Because of the smaller size of breast tissue in males, nipple involvement is seen early in the course of the malignant process, with ulceration in 6% of the patients, discharge in 6%, and retraction in 9%. When there is only bloody nipple discharge without a palpable mass, the diagnosis can be made early and is usually ductal carcinoma in situ of low or intermediate grade.6 Paget’s disease is rare, presenting in only 1% of patients, with a mean age of onset of 60 years, similar to that of other males with breast cancer.7 Axillary lymph node involvement at presentation is more common in men than in women. In rare cases, male breast cancer presented as an occult primary with lymph nodes metastases.8 In summary, clinical presentation extends a spectrum of the most common painless breast mass, or mass with variable symptoms, to the least common metastatic disease.

Clinical evaluation should look specifically for male breast cancers risk factors which are divided into high risk groups such as advanced age, antiandrogens therapy, radiotherapy and hormonal imbalance as in liver failure, and strong family history due to BRCA 2 mutations.9 Low index of suspicion due to the rarity of the disease and poor awareness by both patients and their doctors about
the presence of such a cancer in males have been largely responsible for diagnostic delays with a mean delay time from 6-10 months after the onset of symptoms. More than 40% of males with breast cancer present with stage III/IV disease, and in North Africans, this percentage reaches 50–60%. The tumour-node-metastasis staging system may not be suitable in male breast cancer because of scarce breast tissue and early chest wall and lymphatic spread. However, it is common practice to stage male breast cancer by computed tomography scan of the chest, abdomen, and pelvis.

Radiologic assessment
Mammography can identify malignant breast tumours with a sensitivity of 92-100% and a specificity of 90%. Axillary ultrasound could be helpful in staging since a significant portion of patients have axillary metastases at diagnosis.

A male breast cancer mass may have spicules and irregular margins (figure 1) and can be readily recognised from the surrounding tissue and eccentric position. Microcalcifications are not as common in male breast cancer as in their female counterparts. Skin retraction or ulceration and lymph node involvement are suggestive of male breast cancer.

Male breast ultrasonography shows malignant lesions as solid lesions (figure 2) or complex cystic lesions, both of which mandate biopsy. Ultrasound can be used also for examination of the axillary lymph nodes (figure 3), supraclavicular, infraclavicular, and internal mammary lymph nodes. The ultrasound features of male breast cancer include hypoechoic mass with irregular or indistinct margins, posterior shadowing or posterior acoustic enhancement, architectural distortion with loss of the normal fat-parenchymal interface, and enlarged axillary lymph nodes.

Tissue biopsy
Core biopsy is preferred over fine-needle biopsy because it enables a definitive diagnosis of invasive breast cancer.
The presence of malignant cells on a cytology specimen may be the result of ductal carcinoma in situ rather than invasive disease, and treatment of the two diseases is completely different. In addition, core biopsy yields a tissue sample similar to that of open biopsy without the need for a formal surgical procedure.

**Histopathology**

The most common histological type of male breast cancer is invasive ductal carcinoma, which represents more than 90% of all cases. The other histopathological types of male breast cancer from the most to the least common include ductal carcinoma in situ, adenocarcinoma not otherwise specified (NOS), invasive papillary carcinoma, carcinoma NOS, medullary carcinoma mucinous carcinoma, inflammatory carcinoma, phyllodes tumour, leiomyosarcoma, Paget’s disease, and lobular carcinoma. The rudimentary male breast tissue lacks the terminal lobules and does not differentiate into lobules unless under the influence of high concentrations of endogenous or exogenous oestrogen. The lobular histotype accounts for only 1.5% of invasive cancers. Lobular carcinoma has been reported in men with Klinefelter’s syndrome and surprisingly, in genotypically normal males with no previous history of oestrogen exposure.

Ductal carcinoma in situ of the male breast cancer represents 10% of all cases. Most of these (74%) are papillary carcinomas, usually of low or intermediate grade. All the histological subtypes noted in females are also seen in males; the most prominent patterns being the papillary and cribriform patterns. Much rarer tumour types include invasive papillomas and medullary lesions. The invasive male breast cancers are histologically classified according to the World Health Organisation 2012 criteria. The frequency of histological subtypes differs between males and females, with invasive carcinomas of no special type being by far, the most common subtype (> 90%), followed by invasive papillary carcinoma and invasive micropapillary carcinomas.

Oestrogen receptor positivity has been reported in more than 90% of male breast cancers, with 92–96% being progesterone-receptor positive. Surprisingly, male breast cancers are more hormone receptor-positive than female breast cancers (ER > 90% vs 76% and PR > 75% vs 60%, respectively). The proportion of the male breast cancer expressing the hormone receptors increases with age as in post-menopausal women. HER2 amplification is seen in less than half as frequently in male breast cancer when compared to female breast cancer (5% vs 15%). Subsequently, the most common phenotype seen in male breast cancer is the luminal (ER+ and/or PR+, HER2-) subtype.

**CONCLUSION**

The diagnosis of male breast cancer should follow simple orderly steps similar to female breast cancer diagnosis. Careful attention and good evaluation for breast complaints, especially in high-risk patients, is essential to avoid misdiagnosis. Increased public awareness about the presence of such a cancer in men is warranted to promote seeking care for breast changes in males. The most common clinical picture is a hard retroareolar mass in the left breast in a man in his sixth decade, which is suspicious upon mammography and ultrasonography; its most common pathology is invasive ductal carcinoma in stage II or III.

**DISCLOSURES**

All authors declare no conflicts of interest. No funding or financial support was received.

**REFERENCES**

Dalteparin and anti-Xa: a complex interplay of therapeutic drug monitoring


Department of Internal Medicine, University Medical Centre Utrecht, Utrecht, the Netherlands. Corresponding author: e.d.p.vanbergen@umcutrecht.nl

ABSTRACT

Background: Monitoring low-molecular-weight heparins is generally not required. However, guidelines advise to monitor anti-Xa levels in patients with renal insufficiency or a BMI above 50 and in pregnancy. Measuring anti-Xa levels is a complex challenge since sampling should be performed three to five hours after subcutaneous injection and after steady state concentrations have been reached. Strict compliance is pivotal for justified dose adjustments. Objectives: We questioned compliance to our protocol and performed this study to explore that.

Methods: This retrospective cohort study included patients ≥ 18 years receiving therapeutic dalteparin in a Dutch academic medical centre. Patients with a first anti-Xa level measured between February 23rd and December 30th, 2017 were selected. According to our local guideline, monitoring anti-Xa activity is indicated in patients on therapeutic doses of dalteparin who are pregnant, morbidly obese (BMI > 50), or have renal insufficiency (clearance < 60 ml/min). Accurate sampling was defined as measuring levels after at least three injections (after which a patient may reach steady state) and then four hours after the injection with dalteparin. The frequency of compliance to our protocol was assessed.

Results: We included 158 patients with 396 anti-Xa levels, of which 41% (65/158) of all first anti-Xa levels were drawn without appropriate indication. Almost half, 48% (211/396), were sampled incorrectly and 25% of these (53/211) were followed by a dose adjustment. In total, 74% (293/396) of the samples were not indicated or were taken at the wrong time.

Conclusions: Monitoring anti-Xa levels is a complex clinical challenge. This study showed that non-compliance with recommendations for anti-Xa monitoring was high, often resulting in unjustified dose adjustments.

KEY WORDS

Anticoagulants, compliance, drug monitoring guideline, low-molecular-weight heparin

INTRODUCTION

Anticoagulants are widely used in preventing and treating venous thromboembolism (VTE). Several anticoagulant therapies are available, each with different pharmacodynamic and pharmacokinetic properties. For ambulant use, the recently developed direct oral anticoagulants (DOAC) are increasingly used, mainly as an oral application; in addition, therapeutic drug monitoring (TDM) is not required, in contrast to the classically used coumarin derivates. Anticoagulants are also frequently used in-hospital. Hospitalised patients are classically treated with low-molecular-weight heparins (LMWH), primarily for bridging therapy during a perioperative period or during cancer-associated VTE. The applicability of coumarin derivates is limited because of its teratogenicity during pregnancy and because patients may have altered metabolism during disease in a hospital setting, resulting in unstable plasma-levels. DOACs could be considered an alternative, but safety and optimal use are still subject to current investigation. Moreover, tailored intervention in cases of bleeding is not yet available for all subclasses. For those reasons, many hospitalised patients are still treated with LMWHs. LMWHs are administered as subcutaneous injections once or twice daily and have a predictable anticoagulant dose-response curve. Therefore, LMWHs are prescribed as a fixed dose based on total body weight and monitoring is generally not required. LMWHs are primarily renally excreted. Thus, patients with renal insufficiency and patients with potentially altered pharmacokinetic profiles (mainly obese and pregnant patients) may be subjected
to increased risk of over or under treatment. These patients are usually subjected to TDM by measuring anti-Xa activity. Whether or not these protocols are entirely evidence-based and should be used is also subject to debate. However, as long as these protocols are recommended, appropriate utilisation is important.

Monitoring anti-Xa levels is a complex clinical challenge. Firstly, since peak anti-Xa levels are reached four hrs after subcutaneous administration of LMWH, sampling for anti-Xa measurement should be organised between 3-5 hrs after LMWH injection. Secondly, a steady state is reached after 2-4 subcutaneous injections. Sampling before steady state concentrations are reached leads to unreliable interpretation of plasma levels and subsequent unjustified dose adjustments, therefore compromising its safety with potentially serious consequences such as thrombotic events or bleeding.

Due to its complexity, we hypothesised that compliance to guidelines concerning anti-Xa monitoring is low. We therefore investigated the indications, timing of sampling, and associated dose adjustments in patients receiving dalteparin (once or twice daily administered LMWH) in the University Medical Centre Utrecht (UMCU).

MATERIALS AND METHODS

Patient population
The study population comprised all patients who were 18 years and older and had their first anti-Xa level drawn between February 23rd and December 30th, 2017. Exclusion criteria were anti-Xa levels drawn for monitoring activity of intravenous heparin or DOAC. Since our hospital uses dalteparin as standard LMWH, the few other LMWHs were excluded.

Study design, data source, and collection
We conducted a single-centre retrospective cohort study at the UMCU, an academic hospital in the Netherlands. Data on the first and repeat anti-Xa level measurements of these patients were collected from the laboratory. Clinical data were abstracted from systematically screened medical records by one researcher (EB). The following baseline characteristics were collected on each patient: age, gender, estimated glomerular filtration rate (eGFR); information about continuous venovenous haemofiltration, haemodialfiltration or haemodialysis; information regarding dalteparin included indication, time of dalteparin administration (as registered in the medical file by the nurse), and dosing frequency; indication for anti-Xa monitoring, anti-Xa level, time of sampling (as registered in the medical file by the laboratory), dose adjustments, and reasons for repeat anti-Xa level measurements. Anti-Xa assays were conducted in our laboratory using Liquid Anti-Xa (Diagnostica Stago, United States of America).

Ethics
The Medical Ethics Committee of the UMCU gave permission to perform this study. This study does not fall under the Medical Research Involving Human Subjects Act.

Recommendations for anti-Xa monitoring
According to the ‘Diagnostics and treatment of venous thromboembolism’ guideline of the UMCU, based on the guideline provided by the Dutch Federation for Nephrology, monitoring anti-Xa activity is indicated when patients receive therapeutic doses of dalteparin and are pregnant, morbidly obese (> 150 kg or Body Mass Index (BMI) > 50 kg/m²), or have renal insufficiency (eGFR ≤ 60 mL/min). Peak levels should preferably be measured four hrs after treatment, but at least within 3-5 hrs after LMWH injection and after at least three subcutaneous injections. According to our guideline, patients on therapeutic dalteparin should receive 200 IE/kg per day, preferably in one dose. Physicians can decide to give two doses a day, depending on the risk of bleeding. Patients with an eGFR < 30 ml/min or eGFR 30-60 ml/min start with a normal dose, followed by 50% or 75% of the initial dose, respectively. When dalteparin is used for more than three days, dose adjustment is based on anti-Xa levels. Anti-Xa levels should be 1.0-2.0 U/mL when LMWH is administered once a day and 0.6-1.0 U/mL when administered twice daily.

The guidelines do not recommend anti-Xa monitoring in patients on prophylactic dalteparin, in patients with (suspected) thrombotic or bleeding event, and in patients with a history of renal insufficiency but an eGFR above 60 mL/min at the time of measurement. Additionally, the guidelines do not provide information about the indications for repeat anti-Xa level measurements. As many patients had multiple levels measured, we did examine the reasons for those repeats.

Compliance with recommendations
Medical records were screened for pregnancy, renal insufficiency, and obesity. Anti-Xa level measurements were considered in compliance with the recommendations if the indication was appropriate and if accurate sampling was performed. TDM was considered not in compliance with the recommendations when anti-Xa levels were not sampled 3-5 hrs after subcutaneous injection or if the anti-Xa level was drawn while dalteparin could not have reached a steady state, defined as after less than three injections of dalteparin. Repeat anti-Xa level measurements were classified as appropriate when the previous anti-Xa level was out of range and a dose adjustment was made, when the previous anti-Xa level was...
incorrectly drawn, when there was a significant change (≥10%) in eGFR and the eGFR was below 60 mL/min, or during pregnancy. Incorrect reasons for repetition were thrombotic or bleeding events, restarting LMWH, medical interventions (e.g., surgery), a history of renal insufficiency with eGFR above 60 mL/min at the moment of anti-Xa activity measurement, or otherwise, if the reason for repetition was not clear.

Outcome definitions
The primary outcome was the frequency of non-compliance with the recommendations for anti-Xa monitoring in patients receiving dalteparin. Repeat anti-Xa level measurements were studied to see whether the indication for repetition was appropriate. Secondary outcomes were the consequences for dosage regimens, due to decisions based on these levels.

Statistical analysis
The collected data were entered into a database made with IBM SPSS version 21.0 and frequency analyses were performed. Descriptive statistics were used for demographic data.

RESULTS

Patients
A total of 158 patients with 396 anti-Xa level measurements were included and analysed (figure 1). Baseline characteristics are presented in table 1. This table also shows information regarding patients with an indication for therapeutic dalteparin. Three patients suffered from VTE while using other anticoagulants and were therefore switched to LMWH.

Outcomes
The primary outcome, the frequency of non-compliance with the recommendations for anti-Xa monitoring in patients receiving dalteparin, is illustrated in figure 2. Of all first anti-Xa level measurements, 41% (65/158) had an inappropriate indication (table 2), 36% (142/396) were not drawn as a peak level, and 17% (69/396) were sampled before steady state concentrations were reached. In total, 48% (189/396) were inappropriately sampled, of which, 25% (47/189) were followed by a dose adjustment. Of the repeat anti-Xa level measurements, 41% (97/238)

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>176 patients (432 anti-Xa level measurements)</th>
<th>158 patients (396 anti-Xa level measurements)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in years (IQR)</td>
<td>65 (21)</td>
<td>65 (21)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>94 (60)</td>
<td>94 (60)</td>
</tr>
<tr>
<td>eGFR category, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR &gt; 60</td>
<td>56 (35)</td>
<td>56 (35)</td>
</tr>
<tr>
<td>eGFR 30-60</td>
<td>46 (29)</td>
<td>46 (29)</td>
</tr>
<tr>
<td>eGFR &lt; 30</td>
<td>55 (35)</td>
<td>55 (35)</td>
</tr>
<tr>
<td>CVVH/HD</td>
<td>10 (6)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>LMWH indication, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Anticoagulation during malignancy</td>
<td>48 (30)</td>
<td>48 (30)</td>
</tr>
<tr>
<td>- Bridging (perioperative, pregnancy)</td>
<td>86 (54)</td>
<td>86 (54)</td>
</tr>
<tr>
<td>- Anticoagulation during suspected malignancy</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>- Antiphospholipid syndrome</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>- Inappropriate for DOAC</td>
<td>14 (9)</td>
<td>14 (9)</td>
</tr>
<tr>
<td>- VTE during other anticoagulants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Prophylactic dosing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of LMWH dosing, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Once daily</td>
<td>40 (25)</td>
<td>40 (25)</td>
</tr>
<tr>
<td>- Twice daily</td>
<td>118 (75)</td>
<td>118 (75)</td>
</tr>
</tbody>
</table>

CVVH = continuous venovenous haemofiltration; DOAC = direct oral anticoagulants; eGFR = estimated glomerular filtration rate; HD = haemodialysis; IQR = interquartile range; VTE = venous thromboembolism.
had an incorrect reason for repetition (table 3). Of all initial and repeat anti-Xa level measurements, 74% (293/396) were non-compliant. Of all 396 samples, 118 were followed by a dose adjustment and 64% of these adjustments were based on samples that were either not indicated or performed at the wrong time.

In total, 245 anti-Xa samples were below the target level. No dose adjustment was made in 129/245 patients, the dose was increased in only 98/245 patients, and three anti-Xa level measurements were followed by a dose reduction.

Considering a (suspected) event during therapeutic LMWH as an appropriate indication or reason for repetition, although not stated in the guidelines, 71% (279/396) of all measurements were non-compliant.

**DISCUSSION**

Non-compliance with recommendations for anti-Xa monitoring in patients receiving dalteparin was high in our academic hospital during 2017. To our knowledge, this is the first study reporting on compliance with recommendations for anti-Xa monitoring in patients receiving dalteparin. Because treatment and TDM protocols are relatively complicated, it is highly likely that these findings are not unique to our hospital. In fact, multiple studies looking at TDM compliance of other anticoagulants show very similar results. All of these retrospective, single centre studies were also conducted in large first world country hospitals.13-16

Kufel et al. determined the frequency of correctly drawn anti-Xa levels in patients treated with enoxaparin in accordance with predefined criteria and reported the number of dose adjustments based on incorrectly drawn anti-Xa levels. They included 59 patients with 74 anti-Xa concentrations and concluded that 77% of the anti-Xa levels were incorrectly drawn and often resulted in repeat anti-Xa level sampling; 42% of dose adjustments were based on incorrectly drawn anti-Xa levels.13 Dekker et al. investigated the compliance of prescribers with local guidelines for monitoring of enoxaparin in 67 patients and found that 38 patients (57%) were not appropriately monitored.14 Sacha et al. showed that, in patients treated with enoxaparin, only 44/76 (58%) of the LMWH anti-Xa levels were drawn as a peak level as recommended by the CHEST guidelines.15 Taken together, these three studies also indicate that the majority of anti-Xa measurements is either not indicated or
collected at the wrong time, which resulted in unjustified
dose adjustments. In our centre, patients on a once daily
dose regimen receive dalteparin at 18.00 hrs and patients
on a twice daily dose regime receive dalteparin at 08.00
hrs and 18.00 hrs. Blood is therefore drawn at 12.00 hrs
and 20.00 hrs. This is a burden for the nurses in evening
shifts and for the lab, as these samples arrive late in the
evening. Compliance with protocols requires feasibility to
implement its practical aspects within the work routine of
the nurses and the lab. This again shows us that protocols
that are practically difficult to adhere to are prone to be
incorrectly followed. Even in the setting of our centre (an
academic hospital), compliance is low, informing us that
we either need to drastically reconsider our protocols or
think of alternative solutions.

The studies mentioned above strengthen our results and
support a broader need for anti-Xa protocol evaluation and
adjustment in hospitals around the globe.

The main strength of this study is the completeness of
“real world” data obtained through the laboratory reports
with all anti-Xa levels. Our study also describes the
largest number of patients compared to all other studies
on anti-Xa level monitoring and is the first to describe
monitoring in patients treated with dalteparin.

There are some limitations, however, that need to be
addressed. First, this study had a retrospective design.
This could lead to potential inclusion bias. For example,
the number of patients that were not monitored but
should have been monitored is unknown. Dekker et al.
showed that 18 of the 67 patients (27%) who received
oxaparin had an indication for monitoring according
to their local guideline but were not monitored.14 In
addition, patients with renal failure possibly need routine
dose adjustments based on their eGFR. Kikkert et al.
assessed Dutch antithrombotic treatment strategies
for acute coronary syndrome in light of the European
Society of Cardiology guidelines and showed that dose
adjustments of LMWH therapy for patients with renal
insufficiency were not applied in 71% of the hospitals.15
Compliance to this specific part of the protocol is also
important in LMWH dosage regimens, but this study
focused on TDM and therefore only investigated whether
anti-Xa monitoring and eventually dose adjustments
based on anti-Xa levels were performed correctly. Finally,
we used time of registry to check if peak levels were
monitored, but this registry time does not always reflect
the real time of last administration.

Second, the criteria that identify events as non-compliant
could be debated. Indications for anti-Xa monitoring are
not always registered by treating physicians, which in
our study was classified as non-compliant. However, it is
possible that some of these events were indicated correctly,
and therefore influenced the results.

Third, we identified off-protocol indications that are not
necessarily wrong. For example, several patients were
sampled to check compliance to therapy when they were
admitted to the hospital with a VTE or recurrent VTE.
In this study, we categorised these anti-Xa sampling
indications as incorrect, which can be debated. However,
when we further analysed our data, we found that 71% of
the anti-Xa measurements could still be classified as
non-compliant, even when an event or suspected event is
considered an appropriate indication or reason for anti-Xa
assay repetition.

Another point of discussion are the samples drawn prior to
reaching steady state concentrations with anti-Xa activity
above the upper limit. At this moment, a dose adjustment
can already be made. However, correct dose adjustments
by clinicians can only be made when they are aware of
the exact times of dalteparin administration and blood
sampling, which in practice is usually not the case. In our
cohort, of the 69 patients who were sampled before steady
state concentrations were reached, only four patients had
an anti-Xa activity above the upper limit. None of them
received a dose adjustment.

Another category of questionable compliance is formed
by patients with a fluctuating eGFR. When anti-Xa levels
were measured while the eGFR was above 60 mL/min,
this measurement was classified as incorrect, while the
rational to sample anti-Xa in patients with fluctuating
eGFR is defendable.

In summary, this study showed that non-compliance
with recommendations for anti-Xa monitoring is high,
resulting in unjustified dose adjustments. Although TDM
is straightforward in principle, in practice it is a complex
clinical process, and it is highly likely that the findings in
this study are universal.

To improve large scale anti-Xa monitoring, we recommend
that hospitals reconsider administration and blood
collection times in order to facilitate anti-Xa monitoring
within reasonable working hours, as this will relieve the
burden on shift workers. Education and automatic alerts
will help create awareness and thereby probably increase
compliance. Finally, the outcome of anti-Xa monitoring on
clinical endpoints is questionable. We therefore think that
this practice as a whole should be reconsidered.

In conclusion, we strongly recommend revisiting
in-hospital LMWH drug monitoring protocols and if
applicable, evaluate compliance and awareness.

DISCLOSURES

All authors declare no conflicts of interest. No funding or
financial support was received.
van Bergen et al. Issues with anti-Xa monitoring.

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ABSTRACT

Background: The Press Ganey survey is widely used to evaluate physician and institution quality and performance, with some institutions making their survey results publicly available. However, given its subjective nature, the survey results may be subject to bias regarding physician characteristics, such as race, sex, and specialty, that are unrelated to competence. The goal of this study was to determine if and what physician characteristics influence Press Ganey results.

Methods: In this study, publicly-available information on sex, race, specialty, and Press Ganey results for all physicians with a photograph and a Press Ganey rating at two institutions was collected in June 2018 and compared for difference.

Results: The average Press Ganey rating for the 678 physicians included in the study was 4.73 out of 5. Female physicians had fewer negative comments (0.49 female vs. 0.67 male, p = 0.04) and there was no difference in positive comments or ratings. White physicians had higher ratings (4.74 white vs. 4.71 non-white, p = 0.01), greater number of positive comments (12.3 vs. 10.0, p = 0.008), and fewer negative comments (0.55 vs. 0.80, p = 0.03). Paediatric physicians had lower ratings (4.66 paediatric vs. 4.75 adult, p < 0.001) and fewer positive comments (9.07 paediatric vs. 12.21 adult, p = 0.004).

Conclusions: These results suggest that physician race and specialty choice impact Press Ganey results. Given that neither race nor specialty influence physician competence, this data suggests that the Press Ganey survey is a biased measure of physician quality and should not be used to evaluate physician skill or ability.

KEYWORDS

Evaluation, patient satisfaction, quality assessment, quality improvement

INTRODUCTION

The Press Ganey survey is widely used in the United States to evaluate quality and performance of institutions and physicians. Some hospitals post the results of the survey online to allow patients to explore and select their potential providers. However, the Press Ganey survey is based on the subjective experiences of patients who may be prompted to respond based on a particularly positive or negative experience, and may have their responses modulated by unconscious biases. While data is unclear regarding the influence of physician sex on Press Ganey results, physician specialty choice and race do seem to impact the results, with non-white physicians tending to be rated lower than white physicians.\(^1\)–\(^4\) If bias based on physician characteristics unrelated to medical competence – including sex, race, and specialty – influences Press Ganey results, then the survey results should either be corrected to account for bias, or use of the survey and wide dissemination of the results should be reassessed. The goal of this study was to compare results of the Press Ganey survey for physicians at two institutions and identify any physician factors, if present, that correlated with survey results.

METHODS

The compiled results of Press Ganey surveys posted online were collected for physicians at two hospitals: Wake Forest Baptist Health and Oregon Health & Science University. All physicians with a Press Ganey rating and a photograph were included in the study. Data was collected on physician sex, race, specialty, overall Press Ganey rating, and number and type of comments. Physician sex and race were determined by the author based on name, photograph, and country of origin if listed. Comment type was determined by the author and judged to be positive if the comment complimented the physician in any way or simply listed a positive word such as ‘good’ or ‘great’. Comments were
judged to be negative if they criticised any aspect of the patient’s time with the physician. Comments that did not relate to the physician or complimented or criticised office workflow, staff, or wait times were not counted as positive or negative. Physicians were compared based on sex, race, and specialty on the basis of overall Press Ganey rating and comment type using Welch’s t-test with a significance level of 0.05.

RESULTS

Included in the study were 678 physicians across two institutions. The majority were male (63.3%), white (77.0%), primarily treated adult patients (86.0%), and were in a non-surgical specialty (57.7%). The average Press Ganey rating was 4.73 out of 5; the average number of positive comments was 11.77; and the average number of negative comments was 0.60. As shown in table 1, when compared on the basis of sex, female physicians had a lower average number of negative comments (0.49 female vs. 0.67 male, p = 0.04). No difference was found in average number of ratings (181.0 female vs. 204.2 male, p = 0.12), average rating (4.74 female vs. 4.73 male, p = 0.16), average positive comments (11.82 female vs. 11.75 male, p = 0.94), and average total comments (13.26 female vs. 13.45 male, p = 0.84).

When compared by race, white physicians had higher average ratings than non-white physicians (4.74 white vs. 4.71 non-white, p = 0.01), greater number of positive comments (12.31 white vs. 10.00 non-white, p = 0.008), fewer negative comments (0.55 white vs. 0.80 non-white, p = 0.05), and more comments overall (13.82 white vs. 11.91 non-white, p = 0.03).

When broken down by specialty, physicians in any paediatric specialty had on average, fewer ratings (128.61 paediatrics vs. 206.59 adults, p < 0.001); fewer positive comments (9.07 paediatrics vs. 12.21 adults, p < 0.001); fewer negative comments (0.84 paediatrics vs. 0.57 adults, p = 0.004), and more comments overall (10.64 paediatrics vs. 12.89 adults, p = 0.007).

<table>
<thead>
<tr>
<th>Table 1. Physician characteristics and Press Ganey survey results</th>
</tr>
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<tbody>
<tr>
<td>N</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>P value</td>
</tr>
<tr>
<td>Non-white</td>
</tr>
<tr>
<td>White</td>
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<tr>
<td>P value</td>
</tr>
<tr>
<td>Paediatrics</td>
</tr>
<tr>
<td>Adults</td>
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<tr>
<td>P value</td>
</tr>
<tr>
<td>Adult surgical</td>
</tr>
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<td>Adult non-surgical</td>
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</tr>
<tr>
<td>Paediatric surgical</td>
</tr>
<tr>
<td>Paediatric non-surgical</td>
</tr>
<tr>
<td>P value</td>
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</tbody>
</table>

+/- standard error
P values < 0.05 are bolded
DISCUSSION

The findings of this study suggest that physician characteristics influence Press Ganey survey results. In particular, physician race (white vs. non-white) and specialty choice may have a positive or negative effect on the survey. Physician sex did not appear to affect survey results in this study.

Although there is limited data on the influence of physician characteristics on the Press Ganey survey, this study supports others that have found a bias favouring white physicians and no effect of physician sex, though the latter remains controversial.\textsuperscript{1,3,4} A 2018 cross-sectional study of outpatient gynaecology visits found that female gynaecologists were rated significantly lower than their male counterparts due to their sex alone.\textsuperscript{2} However, a 2017 retrospective observational study found no association between physician race and sex and Press Ganey rating, although white physicians were consistently rated higher and male physicians scored higher than females in certain categories.\textsuperscript{3} This 2017 study also found that physician specialty influences Press Ganey ratings, with obstetricians scoring highest followed by surgeons.

To the author’s knowledge, the current study is the first that examines the differences in Press Ganey ratings between physicians in adult and paediatric specialties. The lower average ratings for paediatric specialties may occur because the parent is often completing the survey rather than the patient, and the parent may be more likely to take offense on behalf of their child if a perceived slight occurred. Physicians and parents also often have differing interpretations of what a child’s medical needs are, and misunderstandings could lead to lower ratings.\textsuperscript{5} For example, a parent observing a physician examining their sick child may be concerned that the physician is upsetting the child or being too aggressive, which could translate into parental dissatisfaction with the physician and subsequent low Press Ganey ratings.

While physician race seems to consistently influence Press Ganey ratings across specialties, sex may have an effect on some specialties more than others, and its effects may need to be analysed on a specialty-by-specialty basis. Regrettably, the race bias that appears to exist across specialties, and the sex biases that may or may not be present, likely represent symptoms of biases and stereotypes present in society as a whole, and thus medicine is unlikely to single-handedly eliminate patient bias towards physicians of particular characteristics. Medicine may be more successful at combatting specialty-specific bias, as there are no competency reasons for why obstetricians or adult specialists should be rated higher than any other type of physician. The origin of these apparent biases may be due to the types of environments in which physicians work and the patient emotions often present there. Obstetricians are part of an often-joyous occasion, and patients’ positive feelings towards the event may translate into positive feelings towards their physician. Likewise, patients may have high regard for surgeons, who are often able to affect dramatic cures or immediate improvements in quality of life. Visits with the internal medicine physician whose treatments take time with often gradual effects, as well as the paediatrician, with whom visits may seem a formality for a healthy child, likely evoke fewer strong positive emotions and thus perhaps a lower rating. Separating patient satisfaction with the physician from patient feelings towards the visit or their condition may be more difficult to impossible, but possible measures could include distributing surveys several weeks or even months after the visit so that any strong emotions surrounding the visit have cooled; or conversely distributing the survey immediately after the visit so that a patient does not forget about an ordinary but satisfactory visit.

That physician specialty and race appear to influence Press Ganey survey results suggests that the survey may not be as unbiased as it was intended to be, and that its results should not be used as a marker of a physician’s skill at his or her job. Given that the average patient is unlikely to select a physician by comparing ratings within a physician’s particular demographic group (e.g., white female paediatric neurologists), it would seem best to remove Press Ganey ratings from public view to avoid selection of a physician based on potentially biased results. These study results also call into question the utility of the Press Ganey survey to institutions as well. While portions of the survey may be useful in identifying system-wide problems, such as long wait times or poor coordination or communication between services, given the apparent bias...
in the survey results, institutions should rethink forming judgments on an individual physician’s competence using Press Ganey results, and that perhaps the survey should remove such questions altogether. Other options to evaluate physician skill could include objective measures, such as incidence of post-operative complications for surgeons, or percentage of patients who have achieved blood pressure or haemoglobin A1c level goals. An example of this is the Medicare Access and Children’s Health Insurance Program (CHIP) Reauthorization Act Merit-based Incentive Payment System, which provides financial incentives and penalties for various measures of healthcare quality.\(^6\) Subjective measures of evaluation could include distributing surveys to not only patients but also support staff and other physicians to gain a better understanding of how a particular physician works with his or her colleagues. Limitations of this study include inclusion of only two institutions and the subjective judgement by the author of comments as positive or negative. There was also minimal to no representation of certain specialties, such as pathology, radiology, hospital medicine, and emergency medicine, due perhaps to lack of distribution of surveys to hospitalised patients, low response rates, or minimal direct patient contact. Future directions include inclusion of more institutions and inclusion of more specialties. The widely used Press Ganey survey may not be free from bias, as demonstrated by non-white physicians and physicians in paediatric specialties scoring lower than their white and adult specialty counterparts. These findings suggest that evaluation of a physician’s competence based on the Press Ganey survey is not valid and that the survey should be redesigned, or perhaps that questions relating to the physician should be removed from the survey entirely to better facilitate improvement of an institution as a whole.

**DISCLOSURES**

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**REFERENCES**

CASE REPORT

Epstein-Barr virus infection or malignant lymphoma – what you see is not what you get

I. De haes1,2*, J. Versluis1, K.H. Lam3, J.L.M. Jongen4, J.K. Doorduijn1, S. Kuipers5

1 Department of Haematology, Erasmus Medical Centre Cancer Institute, Rotterdam, the Netherlands; 2 Department of Internal Medicine, University of Antwerp, Antwerp, Belgium; Department of 3 Pathology, 4 Neurology, Erasmus Medical Centre, Rotterdam, the Netherlands; 5 Department of Internal Medicine, ADRZ Hospital, Goes, the Netherlands.

*Corresponding author: inke.dehaes@student.uantwerpen.be

ABSTRACT

Infectious mononucleosis may mimic lymphoma, both clinically and histopathologically. We present a patient with neurological symptoms and lymphadenopathy, initially diagnosed as Epstein-Barr virus (EBV)-positive angioimmunoblastic T-cell lymphoma (AITL) with cerebrospinal fluid (CSF) localisation based on lymph node pathology and a 30-fold higher EBV load in the CSF compared with serum. However, the patient fully recovered spontaneously and EBV became negative in both CSF and serum, suggestive of a dramatic presentation of EBV meningoencephalitis.

KEY WORDS

Angioimmunoblastic T-cell lymphoma (AITL), central nervous system involvement, Epstein-Barr virus (EBV), mimicking lymphoma

INTRODUCTION

The clinical picture of Epstein-Barr virus (EBV) infection may vary from largely asymptomatic patients to a dramatic clinical course, which may include EBV-related meningoencephalitis. EBV infection and malignant lymphoma share a variety of clinical and pathological features, which may result in an incorrect diagnosis of malignant lymphoma.1-4

We present a patient with an unusual course of EBV infection, who was initially diagnosed with angioimmunoblastic T-cell lymphoma (AITL) with central nervous system (CNS) localisation. This case demonstrates the complexity of the clinical picture and the subsequent use of additional investigations leading to the correct diagnosis.

What was known on this topic?

• AITL and EBV have a complex interaction

• Central nervous system localisation of AITL is rare

What does this add?

• EBV infection may mimic central nervous system involvement of lymphoma.

CASE REPORT

A 51-year-old man without a significant medical history presented with headache, episodic confusion, nausea, vomiting, fatigue, fever, night sweats, and weight loss following a minor head injury. Physical and neurological examination was normal. A computed tomography (CT) scan of the head was normal. The cerebrospinal fluid (CSF) showed 112 x 10⁶/l leukocytes (100% lymphocytes) and an elevated total protein of 1.7 g/l, suggestive of a viral meningoencephalitis, which was treated empirically with intravenous acyclovir. Virological analysis of the CSF showed an EBV deoxyribonucleic acid (DNA) load of 23605 IU/ml, while EBV DNA in serum was 30-fold lower (794 IU/ml). Flow cytometry of the CSF identified primarily T lymphocytes, without clear monoclonality. Serum lactate dehydrogenase was 494 U/l, whereas alanine aminotransaminase and aspartate aminotransaminase were also elevated (194 and 140 U/l, respectively). A positron emission tomography (PET) scan showed diffuse fluor-[18]deoxy-
glucose (FDG) avid lymphadenopathy (cervical, axillary, mediastinal, retroperitoneal, para-iliacal, and inguinal) with splenomegaly. Biopsies of both tonsil and axillary lymph node yielded a pathological preferential/working diagnosis of angioimmunoblastic T-cell lymphoma (AITL) with expression of pan T-cell antigens (CD3, CD4, CD5) and positive EBV-encoded small ribonucleic acids. Pending the results of gene rearrangement studies, the clinical working diagnosis was AITL with CNS localisation and the patient was transferred to a tertiary referral centre for further workup and treatment. Further evaluation with a magnetic resonance imaging scan showed no intracranial abnormalities. In the bone marrow, a reactive polyclonal T-cell population was observed. Repeated CSF analyses revealed a leucocyte count of \(17 \times 10^3/l\) (100% lymphocytes), a total protein of 0.61 g/l, and normal flow cytometry. Strikingly, EBV DNA was negative in both CSF and serum. Upon revision of the lymph node histology, the results of the gene rearrangement analysis demonstrated a polyclonal B-cell and T-cell population. Hence, a watchful waiting approach was adopted. Clinically, the patient completely recovered. In addition, follow-up FDG-PET scan showed quasi-normalisation except for some residual FDG activity in the axillary lymph nodes, confirming the definitive diagnosis of a systemic EBV infection with secondary EBV meningoencephalitis.

**DISCUSSION**

AITL is a rare and aggressive subtype of a peripheral T-cell lymphoma, classified as a nodal T-cell lymphoma with T-foollicular helper phenotype, according to the 2016 World Health Organisation classification.\(^6,7\) It accounts for approximately 1-2% of non-Hodgkin’s lymphoma.\(^8,9\) Central nervous system involvement is rarely reported.\(^8\) AITL has been known to have a complex relationship to EBV.\(^6,7,9-12\) The initiating event of lymphoma development has been suggested to be antigen driven by EBV because EBV-positive B cells are found early in the course of the disease.\(^11\) In addition, it has been established that EBV-positive B cells can present EBV viral proteins to T cells, providing antigenic and costimulatory signals for T-foollicular helper cells which further stimulate B-cell activation creating an immune stimulatory loop.\(^9\) T-cell dysregulation can also be considered as a possible primary pathogenic event. Weiss et al.\(^6\) investigated 23 cases of AITL for the presence of EBV by in situ hybridization and polymerase chain reaction and found EBV in most of the cases. However, most of the EBV-positive cells expressed the B-lineage antigen CD20, while a minority of the EBV-positive cells stained for the T-lineage associated antigen CD43. It has been suggested that the high prevalence of EBV in AITL is a consequence of T-cell dysregulation and decreased immunocompetence as a result of AITL, rather than the cause of the disease.\(^6,12\)

Here, the combination of central nervous symptomatology, lymphadenopathy, positive EBV DNA in serum and CSF, and lymph node histology was very suspicious for AITL. The differential diagnosis included AITL with CNS localisation, AITL with concomitant EBV meningoencephalitis (with EBV infection as primary or secondary event), or a dramatic course of an acute EBV infection with concomitant meningoencephalitis. However, the histology revision demonstrated no convincingly pronounced proliferation of high endothelial venules, no highly expansive proliferation of follicular dendritic cells, and no high number of T cells expressing the programmed cell death protein (PD-1). Moreover, the T-cell receptor gene was not clonally rearranged. The diagnosis of AITL with CNS localisation became even more unlikely, because of spontaneous clinical recovery, vanishing lymphadenopathy, and disappearance of EBV DNA in serum and CSF.

**CONCLUSION**

Severe systemic EBV infection may mimic malignant lymphoma, both clinically and histopathologically. We present a patient suspected of AITL with CNS localisation, due to presentation with neurological symptoms, B symptoms, and lymphadenopathy in combination with a 30-fold increased EBV load in CSF compared with serum. Repeated analysis of CSF together with histopathological re-evaluation and gene rearrangement studies were crucial in finding the correct diagnosis. We recommend an even more extensive and careful diagnostic workup and comprehensive analysis of all the results obtained, when EBV is involved.

**REFERENCES**


A ring-calcified thymoma, mimicking pericardial cyst, precedes pure red cell aplasia for more than 10 years

A case-based overview of pathophysiology

M.A. de Graaf1, Hans Marten Hazelbag2, J. Tim3, A.P. van Rossum4, L.T. Vlasveld1

Departments of 1Internal Medicine, 2Clinical Pathology, 3Radiology, 4Clinical Chemistry, HMC (Haaglanden Medical Centre), the Hague, the Netherlands.
*Corresponding author: m.a.de_graaf@lumc.nl

ABSTRACT

Pure red cell aplasia (PRCA) is a rare disease characterised by anaemia and low reticulocyte count, caused by absence of erythropoiesis in the bone marrow. This report describes a case of a ring-calcified thymoma that led to the development of PRCA. Moreover, we provide an overview on the classification of thymoma and the pathophysiology and treatment of PRCA.

KEY WORDS

Anaemia, pure red cell aplasia, thymoma

INTRODUCTION

Pure red cell aplasia (PRCA) is a rare bone marrow disorder with absence of erythropoiesis, characterised by normocytic or macrocytic anaemia and low reticulocyte count; other cell lineages in the bone marrow are normal.

Congenital PRCA, associated with mutations in ribosomal protein or the GATA1 transcription factor, manifests in infancy and is associated with other congenital abnormalities and predisposition to cancer.1 Recently, PRCA has been described in patients with adenosine deaminase 2 (ADA2) protein deficiency.2 Acquired PRCA is classified as primary or secondary PCRA. Primary PRCA consists of primary auto-antibody-mediated PRCA and primary dysplastic PRCA. Secondary acquired PRCA in adults is mostly idiopathic but may be associated with autoimmune/immunological diseases, solid and haematological tumours, viral (especially parvo B19) and bacterial infections, and a variety of drugs.

PRCA is traditionally thought to be associated with thymoma, although recent studies reveal that only 10-30% of PRCA are associated with thymoma, and that fewer than 5% of patients with thymoma develop PRCA.3,4 Thymoma is either diagnosed during the work-up of PRCA, or PRCA develops during follow-up after thymectomy. We present an 80-year-old man who developed PRCA after living with an existing pericardial-mediastinal mass with ring calcification for more than 10 years, which was identified as a type A thymoma.

What was known on this topic?
Pure red cell aplasia (PRCA) is a rare, but known haematological disorder; its relation to thymoma has previously been described.

What does this add?
This report describes a case where a ring-calcified thymoma preceded PRCA for years. It is a rare case of a ring-calcified type A thymoma, since most lesions are type B/BA. This report further explores the pathophysiology of thymoma and establishes a correlation with PRCA.
CASE REPORT

An 80-year-old male was referred to us with complaints of anaemia one year after chemo-radiation treatment for T1N2M0 squamous pulmonary carcinoma. At that time, his haemoglobin (Hb) was 14.8 g/dl (12.8-16.8) and radiological examination revealed an additional calcified pericardial-mediastinal mass (figure 1A-D), which was unaltered compared to 11 years earlier. The patient complained of shortness of breath at exercise. Physical examination was unremarkable. Laboratory examination revealed Hb 7.3 g/dl, mean corpuscular volume 102 fl (83-100), reticulocyte count 6.7 x 10⁶/l (25-120), 0.3%, with normal leucocyte and thrombocyte counts. Serum vitamin B12 and folic acid were normal, serum ferritin was 949 µg/l (30-300), and erythropoietin concentration was 239 U/l (4.4-15.8). There were no signs of haemolysis, and immunoglobulins levels were normal. Virologic testing showed no abnormalities and patient did not use any medication associated with bone marrow suppression or anaemia. Bone marrow examination revealed absent erythropoiesis, normal myelopoiesis and megakaryopoiesis (figure 2A, B), and abundant stainable iron. Cytogenetic examination showed normal male karyotype. PRCA was diagnosed and treatment with prednisone (1 mg/kg, resulting in a daily dose of 60 mg) was started without restoration of the erythropoiesis. Treatment with cyclosporine was considered, and refused by the patient. The patient was unfit for surgical resection and died of pneumonia shortly after. Autopsy identified an 8 x 6 cm calcified mass which was easily separated from both the pericardial sac and the surrounding lung tissue.
De Graaf et al. Pathophysiology and treatment of PRCA.

DISCUSSION

Thymoma is a rare (incidence 0.13 per 100,000) epithelial mediastinal tumour of the thymus. There are no well-defined radiological and histological criteria to differentiate between benign and malignant variants. Invasion into the surrounding vasculature, lymphatics, and adjacent structures are considered as malignant features. The current World Health Organisation classification stratifies thymoma based on the ratio between lymphocytes and epithelial cells. Type A thymoma tumours consist of thymic epithelial cells with a spindle shape (formerly known as spindle-cell tumour or medullary thymoma) without nuclear atypia and absent lymphocytes. Type AB thymoma resembles the histology of type A thymoma but have areas with reactive lymphocytes. The histology of type B1 tumour resembles a normal thymus cortex with round epithelial cells and abundant lymphocytic infiltration. Type B2 tumours have plump cells with vesicular nuclei and heavy populations of lymphocytes. Type B3 (atypical thymoma or well-differentiated thymic carcinoma) consists of round epithelial cells with mild atypia and very few lymphocytes. Type C thymomas or thymic carcinoma have clear-cut cytological atypia and absent cytoarchi-

(figure 2C). After decalcification, a type A thymoma was diagnosed upon microscopic examination (figure 2D).
tectural features. Types A, AB, and B1 thymoma are mostly considered benign and type B2 and B3 have high risk for malignancy. As observed with a CT scan, thymoma typically has smooth or lobulated contours with mostly homogeneous contrast enhancement. Invasiveness is difficult to establish. Size, irregularity, the presence of cystic, necrotic, or calcified areas within the tumour and fat infiltration around the tumour are reported as signs of high-risk or high-stage thymoma. While calcification of the thymoma on a CT scan is not uncommon and associated with the presence of high-risk and malignant thymoma, ring calcification as observed in our patient is rare and associated with type B thymoma.

Thymoma is associated with a broad spectrum of autoimmune diseases such as myasthenia gravis and autoimmune cytopenia, including PRCA and Good’s syndrome (immune deficiency associated with hypogammaglobulinaemia). Autoimmune diseases are usually diagnosed shortly after or concomitant with the detection of the thymoma. In 15% of patients, thymoma may precede autoimmune diseases with a median of approximately a year, and nearly 10% of patients develop autoimmune diseases after thymectomy. Thymoma-associated autoimmune diseases may be related to the histopathologic subtype. Myasthenia gravis is commonly observed in types AB and B thymomas, whereas Good’s syndrome is strongly associated with types A and AB thymoma. PRCA is mostly found in type A thymoma, as in our patient. The mechanism of autoimmunity in thymoma-associated autoimmune diseases is complex and heterogeneous. While in myasthenia gravis, humoral immunity plays a central role, the destruction of the erythroid progenitor or precursor cells, characteristic for PRCA is primarily mediated by autoreactive T cells, although insights are emerging on the role of auto-antibodies as well. Treatment of PRCA is typically focused on the inhibition of these T cells and include prednisolone, cyclosporin, methotrexate, and alemtuzumab. In thymoma-associated PRCA, resection of the thymoma seems a logical cure for PRCA resulting in remission rates of approximately 30% after resection. In a relatively large number of case series, 12 out of 13 patients with both thymoma and PRCA underwent surgical excision and none of those patients experienced complete remission of the associated PCRA. Thus, the majority of patients still required immunosuppressive therapy after resection. Prednisolone has a reported response rate of 30-60% in idiopathic and thymoma-associated PRCA. Small studies revealed a high response rate for cyclosporine. Finally, successful treatment with an anti-CD20 monoclonal antibody (Rituximab) has been described.

**CONCLUSION**

This report describes a unique patient with a PRCA that was preceded for at least 10 years by a highly metabolic ring-calcified pericardial mass, which was identified as a type A thymoma at autopsy.
PHOTO QUIZ

Is that massive effusion in the right pleural cavity?

Z-G. Zhou *, J. Yang, F. Huang

Department of Thoracic Surgery, The Third Hospital of Hebei Medical University, Shijiazhuang, China.
*Corresponding author: 1205888646@qq.com

CASE REPORT

A 44-year-old woman presented to the thoracic surgery department with a one-day history of chest distress and pain in the right side of her chest. The results of the physical examination were notable for rib crowding on the right, a mild scoliosis with convexity of spinal curvature towards the left, heart sounds best heard on the right side of the chest, and low breathing sounds on the right. There was a massive hydrothorax as seen by chest X-ray (figure 1). A computed tomography (CT) scan of the thorax was made (figure 2).

WHAT IS YOUR DIAGNOSIS?

See page 378 for the answer to this photo quiz.

Figure 1. X-ray revealing massive pleural effusion in the right chest

Figure 2. CT scan revealing pulmonary agenesis

CT = computed tomography
DIAGNOSIS

The diagnosis is pulmonary hypoplasia. This is a rare developmental disorder, and right lung agenesis is considered rarer than its left-sided counterpart. Up to 50% of all cases are associated with cardiac, genitourinary, gastrointestinal, and musculoskeletal anomalies, and the outcome of patients with cardiovascular anomalies is reported to be poor. This condition is often diagnosed in childhood but may be delayed until adulthood in the absence of comorbid anomalies. Presentations vary from clinically asymptomatic to those presenting with respiratory distress, cyanosis, or symptomatology related to the associated anomalies in the genitourinary or musculoskeletal systems. Several syndromes such as Goldenhar syndrome, lung agenesis, congenital heart defects, thumb anomalies syndrome, and Scimitar syndrome are associated with pulmonary agenesis. The importance of identifying this is manifold. First, the radiological findings may appear to be similar to pneumonia, with cases of lung agenesis wrongly managed as pneumonia, as often reported in literature. Second, the finding of lung agenesis should prompt a search for other associated anomalies, which may contribute to the burden of comorbidities. Finally, the presence of lung agenesis may predispose the individual to recurrent respiratory infections and its sequelae; hence, appropriate preventive measures could prove to be beneficial to this set of patients. Chest X-ray examination alone may lead to mis-diagnosis of pulmonary hypoplasia. Multi-slice spiral CT examination has the advantages including continuous and rapid scanning imaging, volume data collection, excellent multi-axial plane, and three-dimensional reconstruction images. It can clearly show the structures of pulmonary blood vessels and bronchi, and is easy to operate with high accuracy. It is therefore considered as the preferred diagnostic method for congenital pulmonary dysplasia. Fiberoptic bronchoscope can also be used as an auxiliary diagnostic method for this disease, which can show the degree of hypoplasia, such as the blind end and stenosis of the diseased bronchus. Treatment is conservative with very little role for surgery in aplasia or agenesis. Prognosis largely depends on the functional integrity of the remnant lung as well as the presence of other comorbidities.

DISCLOSURES

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REFERENCES

PHOTO QUIZ

An unusual complication of pregnancy

B. van Erven*, L. de Wit-Zuurendonk², E. Laupman-Koedam³, L. Nieuwenhuizen¹

Departments of ¹Internal Medicine, ²Gynaecology, ³Radiology, Maxima Medical Centre, Veldhoven, the Netherlands. *Corresponding author: britt.van.erven@mmc.nl

CASE REPORT

A 33-year-old female was referred to the Department of Gynaecology because of an aberrant ultrasound obtained by her obstetrician. She presented at eight weeks gestation with her fourth pregnancy. Previous pregnancies were uncomplicated. She felt otherwise well. Ultrasound demonstrated an intact gravidity and a 1.0 cm x 1.3 cm round echogenic structure on the right side of the uterus, which seemed to be located in a dilated vein (figure 1).

WHAT IS YOUR DIAGNOSIS?

See page 380 for the answer to this photo quiz.

Figure 1. Pelvic ultrasound showing a 1.0 x 1.3 cm round echogenic structure on the right side of the uterus (upper panel) with absence of flow as confirmed by Doppler (lower panel)
**DIAGNOSIS**

This patient has an asymptomatic ovarian vein thrombosis (OVT) of the right ovarian vein. This is a rare and potentially serious condition, estimated to complicate 0.01-0.05% of deliveries.\(^1,2\) Thrombus formation in one or both ovarian veins results from a combination of a hypercoagulable state, venous stasis due to compression of the ovarian veins and inferior vena cava, and endothelial trauma. Women are typically affected in the postpartum period. Only 2-5% of patients develop OVT during pregnancy.\(^1,2\) In cases that are not pregnancy-related, the possibility of an underlying malignancy should be considered, as this constitutes the other most potent risk factor.\(^3\) Whether OVT is more frequent in females with thrombophilic disorders remains to be elucidated. Thrombophilia testing did not reveal any significant abnormalities in our patient.

Clinical signs and symptoms of this disorder, including acute lower abdominal pain and fever, are nonspecific and often resemble acute appendicitis. Asymptomatic cases (i.e., incidentally detected upon imaging) seem quite common, e.g., after vaginal or caesarean delivery or gynaecological surgery, and may be a benign condition in non-pregnant females.\(^1\) If detected during pregnancy, however, it constitutes a risk factor for gestational complications, such as septic abortion.\(^4\) Other potential complications of OVT are significant as well, including thrombus extension to the inferior vena cava or renal veins, sepsis, and pulmonary embolism.

The diagnosis relies on careful examination of radiographic findings. Though pelvic magnetic resonance imaging has the highest sensitivity and specificity, computed tomography or ultrasonography with Doppler constitute proper alternatives and may be more practical in many cases.\(^1\)

Due to a paucity of data on the natural disease course and the efficacy of different treatment regimens, many questions exist regarding optimal management of OVT. Anticoagulation therapy forms the cornerstone of therapy, and treatment protocols for other types of venous thromboembolisms (e.g., deep vein thrombosis) are generally applied. In the absence of thrombus extension, infection, or pulmonary embolism, asymptomatic OVT may not require treatment, since spontaneous thrombus resolution has been observed.\(^1\) In pregnant women, however, even asymptomatic cases warrant anticoagulation therapy in order to prevent gestational complications. Therefore, our patient was treated with low molecular weight heparin throughout pregnancy. A repeat ultrasound postpartum showed complete resolution of the thrombus, whereupon anticoagulation was discontinued.

**DISCLOSURES**

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