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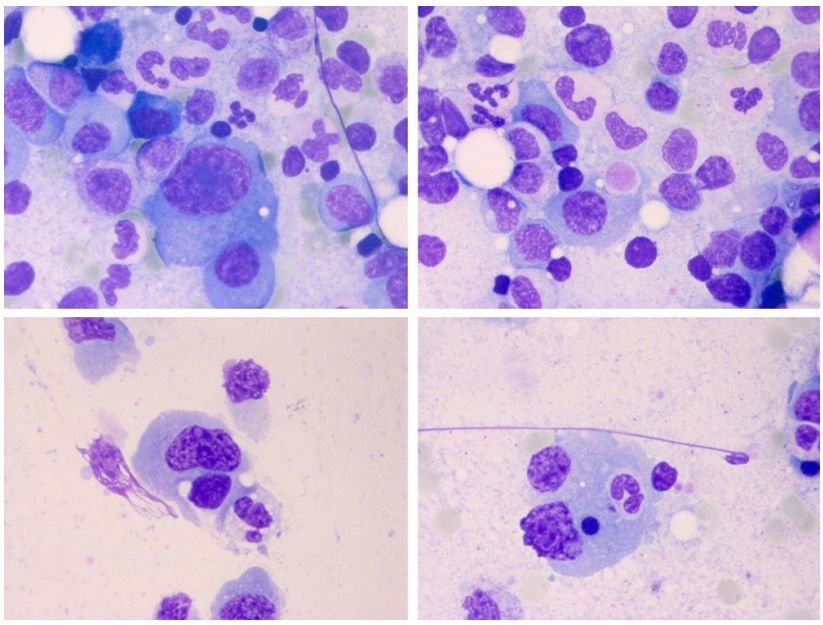

Bone marrow aspirate showing neoplastic plasma cells: what is your diagnosis?

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Contents

EDITORIAL

The paramount importance of pattern recognition in auto-inflammatory diseases in reducing time to diagnosis

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Diagnosis of Familial Mediterranean Fever (FMF) is often delayed, as illustrated by Hageman et al.[1] The authors' message that the diagnostic delay in Amsterdam is comparable with the that in Mediterranean regions where the disease is more prevalent is somewhat reassuring for clinicians working in the Netherlands. However, the delay to diagnosis is still long, more than eight years. In the reported manuscript, the disease severity score was mild in more than half of the patients studied (55%), the majority (more than 90%) reported peritonitis, and more than 30% of patients underwent unnecessary abdominal surgery. Only one patient reported chronic sequela (amyloidosis). If recognized, treatment witch colchicine, the inexpensive first-line treatment for FMF, was effective.

The long-term complication rate in the reported study by Hageman et al.[1] was low, which may reflect the relatively mild disease severity in the population studied. However, if left unrecognized, and in more severe disease cases, the chronic sequelae of FMF can be devastating. Amyloid deposition may lead to end-organ damage such as kidney failure and cardiomyopathy. None of the FMF patients reported in the study of Hageman et al[1] needed second-line therapy. In case of failure of or intolerance for colchicine, second-line therapy, such as anti-interleukin-1 (IL-1) is generally effective.[2]

FMF is the most common auto-inflammatory disease. These conditions are caused by genetic mutations in molecules involved in regulating the innate immune response. Kastner et al. defined the concept of auto-inflammation as an "abnormally increased inflammation, mediated predominantly by the cells and molecules of the innate immune system, with a significant host predisposition".[3] Initially-recognized auto-inflammatory diseases include, in addition to FMF, other periodic fever syndromes such as TNF-receptor-associated periodic fever syndrome (TRAPS), hyperIgD with periodic fever syndrome (HIDS), and cryopyrin-associated periodic syndrome (CAPS).[3] These entities share the clinical hallmarks of fever and other signs and symptoms such as rash, arthralgia, myalgia, and lymphadenopathy with an autosomal inheritance and the feared complication of amyloid deposition. Among these diseases, the efficacy of anti-IL-1 treatment suggests a major role of IL-1 in their pathogenesis.[4] More recently, improved genetic sequencing has led to the discovery of a spectrum of auto-inflammatory syndromes, in which fever may be less pronounced and aspects of auto-immunity or immunodeficiency are part of the phenotype, broadening the clinical and immunological phenotypic spectra seen in these disorders.[5] For example, a genetic defect through which macrophages are skewed towards a pro-inflammatory state underlies the phenotype adenosine-deaminase 2 (ADA2) deficiency, a spectrum of vascular and inflammatory phenotypes, ranging from early-onset recurrent stroke to systemic vasculopathy or vasculitis and immune deficiency.[6]

Early and correct diagnosis is sometimes difficult in auto-inflammatory disease given the variety of clinical signs and symptoms which also often overlap. Auto-inflammatory genetic screening panels help in defining the disease. Furthermore, mosaicism analysis indicates that a lower proportion of mutated alleles is of clinical importance in auto-inflammatory diseases, such as CAPS.[7]

International resources in the field of auto-inflammatory diseases are the International Society of Systemic Auto-Inflammatory Diseases (ISSAID), which, among others, organizes biannual meetings to share insights in the recognition of new disease entities; the EUROFEVER project, https://www.printo.it/eurofever/, which aims at

classifying auto-inflammatory diseases,[8] providing insight into the burden of disease and in supports increased awareness; and INFEVERS (Internet periodic FEVERS), a registry of hereditary auto-inflammatory disorders mutations, https://infevers.umai-montpellier.fr/web/. From the patients' perspective, the Auto-inflammatory Alliance promotes awareness and improved care for people with auto-inflammatory diseases, http://www.autoinflammatory.org/.

Pattern recognition is of paramount importance in reducing the time to diagnosis in auto-inflammatory diseases. The competence of physicians able to recognize disease based on a pattern is to a large extent determined by their clinical experience.[9] Being exposed to auto-inflammatory disease phenotypes through studies like Hageman et al[1] is therefore essential for physicians.

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REVIEW

Point-of-care Ultrasound (PoCUS) for the internist in Acute Medicine: a uniform curriculum

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ABSTRACT

The use of Point-of-care Ultrasound (PoCUS) is rapidly increasing in internal medicine as it is useful in the primary assessment of acutely ill internal medicine patients for enhanced diagnostics and resuscitation. PoCUS can be taught in a modular fashion including basic core applications and advanced applications which can be combined for a symptom-based approach. Several PoCUS curriculum guidelines, especially for emergency medicine, exist throughout the world but a clear Dutch guideline for internists has not been developed. In this review we propose 'core' ultrasound competencies for internists that may also be incorporated into the European Training Requirements Internal Medicine. We suggest the use of an Entrustable Professional Activities (EPA) competency-based training system with EPAs specifically designed for ultrasound.

KEYWORDS

PoCUS, point-of-care ultrasound, ultrasound for internists, ultrasound curriculum, EPA

HIGHLIGHTS

- Point-of-care ultrasound (PoCUS) is an emerging important diagnostic tool for internists
- A uniform Dutch guideline for PoCUS education has not been developed
- An ultrasound curriculum should include description of core ultrasound applications and the process of training and achieving competency
- Ultrasound competency can be assessed using specifically designed Entrustable Professional Activities (EPAs)

INTRODUCTION

Point-of-care Ultrasound (PoCUS) is defined as 'diagnostic or procedural guidance ultrasound that is performed by a clinician during a patient encounter to help guide the evaluation and management of the patient'.[1] This technique is useful in the primary assessment of acutely ill internal medicine patients and enhances diagnostics and resuscitation as it adds clinical data which cannot be obtained by physical examination.[2] This 'stethoscope of the 21th century' is quickly developing, is easily accessible with improved portability, produces images of increasing quality, and is more affordable; however, the diagnostic performance is largely operator-dependent and it is not known how many PoCUS exams a sonographer needs to perform to obtain reliable results.[3] Medical treatment decisions can be guided by ultrasound results; therefore, it is essential that these results are trustworthy. In the Netherlands, ultrasound was first advocated in 2012 as a useful complementary skill for internists in the management of acutely medically ill patients.[4] Today, mandatory PoCUS training is included in the education of internists as stated by the Dutch internal medicine federation (Nederlands Internisten Vereniging, NIV) and a national training program that is currently under development.[5] However, there are not enough ultrasound experts to provide education to all internal medicine residents, and it is questionable if every internist should be fully competent for every PoCUS indication. Regardless, proper training is critical for both current and future ultrasound applications within internal medicine.

Table 1. *Core emergency ultrasound applications*

Trauma (eFAST, extended Focused Assessment with Sonography in Trauma; free fluid)
Pregnancy (ectopic or intra-uterine pregnancy)
Cardiac/haemodynamic assessment (contractility, pericardial effusion/tamponade, central venous volume status)
Abdominal aorta (detection of aneurysm)
Airway/thoracic (pleural effusion, pneumothorax, interstitial disorders, endotracheal tube placement)
Biliary (cholecystitis, gallstones)
Urinary tract (hydronephrosis, bladder status)
Deep vein thrombosis
Soft-tissue/Musculoskeletal (infection, foreign bodies, masses/abscess, fractures, joint effusions, tendon injuries)
Ocular (retinal detachment, dislocations, optic nerve)
Bowel (appendicitis, bowel obstruction, pneumoperitoneum, diverticulitis, masses, hernias)
Procedural guidance (venous access, thoracentesis, paracentesis, joint aspiration)
Adapted from American College of Emergency Physicians[3]

Table 2. *Core ultrasound applications for internal medicine*

Core ultrasound application	Assessment	Transducer	Probe placement
Vena cava	Diameter and collapsibility	Cardiac or abdominal	Subxyphoid longitudinal hepatic view
Free fluid	Hepatorenal recess (RUQ) Splenorenal recess (LUQ) Recto-uterine or recto-vesical pouch (pelvic)	Abdominal	Right anterior axillary line7-9th intercostal space Left posterior axillary line 5-7th intercostal Suprapubic transverse position
Basic abdominal ultrasound	Renal ultrasound - Presence or absence of hydronephrosis Bladder - Urinary retention Aorta - Aneurysm Gallbladder - Gallstones - Cholecystitis	Abdominal	Mid-axillary line (right side) and posterior axillary line (left side) Suprapubic transverse and longitudinal position Subcostal longitudinal and transverse position Right subcostal margin longitudinal and transverse position
Basic cardiac ultrasound	Global assessment of cardiac function Pericardial effusion Right ventricular strain	Cardiac	PLAX, PSAX, Apical 4-chamber Subxyphoid 4-chamber PSAX, Apical 4-chamber
Deep vein thrombosis	3-points compressions of femoral and popliteal vein	Linear	Common femoral vein at branching of GSV and beyond branching to SFV and DFV Popliteal fossa for popliteal vein
Pulmonary ultrasound	Pleural line Interstitial syndromes Pleural fluid	Linear Abdominal Linear	Intercostal space Intercostal space, PLAPS Dorsal intercostal
Procedural assistance	Thoracic and abdominal paracentesis (central) venous access	Linear	Varies

RUQ = Right upper quadrant; LUQ = Left upper quadrant; PLAX = parasternal long axis; PSAX = parasternal short axi; GSV = greater saphenous vein; SFV = superficial femoral vein; DFV = deep femoral vein; PLAPS = posterolateral alveolar and/or pleural syndrome

Existing ultrasound curricula for emergency medicine physicians can be used as guidelines to develop an ultrasound curriculum for internists. For example, the American College of Emergency Physicians (ACEP) has published a revised policy statement on ultrasound guidelines in which they define 12 core PoCUS applications with proven benefit (table 1).[6]

The International Federation for Emergency Medicine (IFEM) has published a similar PoCUS curriculum guideline which describes the content of an ultrasound program and the method for training and practice.[1] In Italy, the ultrasound training program for internal medicine residents consists of a two-step level of competence concerning a variety of clinical presentations and diagnosis divided into five modules.[7] Other European countries have ultrasound training programs as well but these programs do not meet the needs of an ultrasound curriculum as defined by the Dutch Internal Medicine Federation.[8,9] The content of a PoCUS curriculum is determined by regional and national differences as it should be relevant to local and national practice. Therefore, an ultrasound curriculum relevant for internists in the Netherlands is needed. This includes selecting the most relevant core applications for internists and describing how competency in ultrasound is obtained. Achieving competency consists of initial introduction and basic training in ultrasound, gaining experience, assessing competency, and staying competent. In this article, we propose a foundation for a Dutch ultrasound curriculum for internists, especially for internists specialised in acute medicine, but this may be easily used for other specialties within internal medicine. It can also be incorporated into the European Training Requirements Internal Medicine that has been recently published.[10] Furthermore, we describe the necessary steps to become competent in ultrasound.

FOUNDATION FOR ACUTE INTERNAL MEDICINE ULTRASOUND CURRICULUM

We suggest core applications for internists treating acutely ill patients in the Emergency Department (ED) or the ward. These suggestions are based on international guidelines for the development of ultrasound curricula in emergency medicine (see table 2).

Key issues include: 1. general ultrasound knowledge, 2. choosing core applications, 3. integrating PoCUS into clinical decision-making, 4. training, and 5. achieving and maintaining competency.

1. General ultrasound knowledge

The novice sonographer must obtain a basic understanding of ultrasound. [1,6] This includes physics and anatomy, basic 'knobology' (the functionality of controls on an instrument as relevant to their application; how does the machine work), image recording, knowledge of artefacts, basic principles of Doppler ultrasound, characteristics of different probes, and image interpretation.[11] The operator must also be aware of limitations with ultrasound, for example, using caution in cases of inadequate image requisition or lower resolution when using handheld devices; and finally, operators must know their own limitations in skills and interpretation. The concept of PoCUS is to focus on specific, mostly yes-or-no questions for critical conditions in the acute setting.[12] It is mainly used to rule in disease, and is less suited to rule out disease due to lower sensitivity than specificity for several conditions ("when you don't see it, it might still be there"), but this may differ for each core application. For example, cardiac tamponade is safely ruled out if pericardial effusion is not observed. This is how PoCUS differs from structural comprehensive ultrasound examinations performed by radiologists or cardiologists, which include extensive and detailed organ evaluation.
Acquiring a basic understanding can be achieved using multiple educational modalities including lectures, readings, online education modules, and practical hands-on sessions. General ultrasound knowledge is a mandatory basic skill for every core application.

2. Core and enhanced applications

PoCUS can be divided into diagnostic or procedural applications.[1,6] Diagnostic applications can be single area (for example, assessment of the kidneys for hydronephrosis) or combined areas (for example, Rapid Ultrasound in Shock including ultrasound of the heart, the inferior vena cava, and signs for deep vein thrombosis).[13] Examples of procedural applications are ultrasound-guided paracentesis and venous access. It is important to determine what applications will be core applications and meet the needs of the local practice. These core applications can be complemented with a variety of specialty applications depending on individual preferences and local needs. Core applications should be relatively easy to learn, rapid to perform, be frequently encountered, and preferably have a binary yes/no question. It is relevant to know the specific diagnostic performance of ultrasound for each core application. We believe the following core applications are most useful (table 2) for internists who provide care for acute medically ill patients at the emergency department (ED) and also for those caring for acutely deteriorating patients on the ward:

Inferior vena cava (IVC)
Determination of the IVC diameter and the IVC collapsibility index reflects right atrial pressure, and

can be used as a surrogate marker for central venous pressure (CVP).[14-16] A high caval index (collapse > 50% in spontaneous breathing patients during inspiration) reflects a low CVP, whereas a wide diameter (> 2.5 cm) with no signs of respiratory variation reflects a high CVP. In this way, the caval index can aid in estimation of fluid balance and with repeated measurements guiding fluid management of patients with (undifferentiated) shock.[17]

Assessment of free fluid

This assessment requires a structured approach to look for signs of free fluid in three predefined regions:

- right upper quadrant including the hepatorenal recess (Morison's pouch), point of right liver lobe and subdiaphragmic area.
- left upper quadrant including splenorenal recess (Koller pouch) and subdiaphragmic area.
- lower abdominal including recto-uterine or recto-vesical pouch.

Findings of free fluid can aid in diagnosing ascites or blood (ruptured aneurysm/extra-uterine pregnancy). Using PoCUS reduces the risk of complications from abdominal paracentesis by 68% and makes a focused aspiration of smaller amounts of free fluid possible compared with 'blind' paracentesis.[18]

Basic abdominal ultrasound

This includes renal, bladder, abdominal aorta, and gallbladder ultrasound. Acute (on chronic) kidney injury (AKI) is a common problem in general internal medicine, and although postrenal causes of AKI are infrequent and often suggested by medical history, the finding of hydronephrosis can significantly impact clinical management. Grading of hydronephrosis can be challenging, but interpreting a binary yes or no question (presence/absence of hydronephrosis) in PoCUS is relatively easy to learn with fair sensitivity (85%) and specificity (71%).[19] If hydronephrosis is present, an ultrasound of the bladder should include bladder volume measurement to determine the level of urinary tract obstruction. Enhanced renal PoCUS skills may include kidney measurements and identifying signs of inflammation.

Acute abdominal pain is another main reason for ED visits. An abdominal aortic aneurysm (aorta > 3 cm maximum diameter) is an important diagnosis to be ruled out, and can be simply done with ultrasound; even non-radiologists can perform this with high diagnostic accuracy.[20] The presence of cholelithiasis and signs of cholecystitis can be reliably investigated with PoCUS,[21] as gallstones are seen as hyperechogenic structures with shadowing. There is a high suspicion of cholecystitis with a sonographic Murphy's sign (abdominal tenderness from pressure of the ultrasound probe over the visualized gallbladder), gallbladder wall thickening (wall > 3 mm), and pericholecystic fluid, especially in the presence of cholelithiasis. Basic abdominal ultrasound can be enhanced with multiple specialty applications including pancreas ultrasound, liver ultrasound, bowel and appendix ultrasound, genitourinary ultrasound, or vascular ultrasound, depending on local expertise, hospital policy and individual patient needs.

Basic cardiac ultrasound

Comprehensive cardiac ultrasound can be a difficult exam, but a simplified focused cardiac ultrasound can be learned with high sensitivity and specificity for binary questions, comparable to cardiologist-performed ultrasound.[22] These binary questions include looking for pericardial effusion (sensitivity 86%, specificity 86%), signs of right ventricular enlargement (sensitivity 93%, specificity 98%), and making a global assessment of the left ventricular function (normal or low, sensitivity 89%, specificity 96%). Internal medicine residents have been also able to identify left ventricular systolic dysfunction with high sensitivity and specificity (both 94%) after limited training.[23] These findings can assist in the differential diagnosis of shock, for example, obstructive shock in massive pulmonary embolism and pericardial effusion/tamponade, or cardiogenic shock in case of severely reduced left ventricular function.

Deep vein thrombosis (DVT)

Multiple studies have shown acceptable diagnostic accuracy of non-radiologists compared to radiologists (sensitivity and specificity 96%).[24] Three-region compression sonography is performed assessing the common femoral vein at the branching of the greater saphenous vein, after branching to the superficial and deep femoral vein, and at the level of the popliteal fossa for the popliteal vein. The inability to fully compress the vein is the main criterion for DVT. Another sign can be reduced flow assessed with colour flow. This core application is also part of the assessment of a patient with shortness of breath or undifferentiated shock. The finding of DVT in this clinical presentation is highly suggestive of a potentially massive pulmonary embolism.

Pulmonary ultrasound

Shortness of breath is a frequently encountered clinical problem with a large differential diagnosis. Lung ultrasound can identify pneumothorax, interstitial syndromes with excess interstitial fluid like pulmonary edema, pneumonia, or pleural fluid.[25,26] A widely used protocol for structured lung ultrasound is the Bedside Lung Ultrasound in Emergency (BLUE) Protocol, which was published in 2008.[27] In this protocol, the pleural line is reviewed, which can be seen as lung sliding with each respiration originating from the movement of the visceral and parietal pleura.

The presence of lung sliding excludes a pneumothorax whereas identifying the lung point (the point where the visceral pleura separates from the parietal pleural at the margin of a pneumothorax) is pathognomonic for a pneumothorax. The pulmonary parenchyma is aerated in healthy patients which blocks ultrasound signals at the pleural line. With ultrasound, this induces a reverberation artefact of the pleural line and this is seen as repetitive horizontal lines called A-lines. When interstitial fluid is present (for instance pulmonary edema or pneumonia) these A-lines are erased by vertical, hyperechoic, well-defined comet-tail like lines, arising from the pleural line and traversing the entire screen to the bottom, called B-lines. Other findings may include an- or hypoechogenic fluid (pleural fluid) or signs of pneumonia. Lung ultrasound can assist in fluid resuscitation as emerging bilateral B-lines can indicate fluid overload/pulmonary edema.

Procedural assistance

PoCUS is widely used to guide a variety of procedures, including thoracic and abdominal paracentesis, central line placement, or venous access.

3. Clinical decision making

The aforementioned core applications can be taught in modular fashion. When these individual competences are mastered, they can be combined in the work up of various clinical presentations, including a patient with shock, shortness of breath, and acute abdominal pain.

Shock

A patient with undifferentiated shock should be assessed with the Rapid Ultrasound in Shock (RUSH) protocol.[28] According to this three-part protocol, 'the pump', 'the tank' and 'the pipes' are assessed. 'The pump' represents the heart (contractility, pericardial effusion, right ventricular enlargement, and potentially chamber size); 'the tank' represents vascular volume and includes the IVC, lung ultrasound, and abdominal assessment for free fluid; 'the pipes' denote the evaluation of the large vessels for rupture or occlusion (aorta and deep venous thrombosis). Combining these three steps generally illustrates to a more specific group of shock (obstructive, distributive, hypovolemic, or cardiogenic shock).

Shortness of breath

Another example of combining these core applications is during the assessment of a patient with shortness of breath. Evaluation of cardiac function and lung ultrasound may show signs of intrapulmonary edema (B-lines) and a severely impaired ventricular function. An enlarged right ventricle and a wide IVC with absence of collapse may suggest pulmonary embolism requiring a deep vein ultrasound absolutely necessary to search for DVT.

Abdominal pain

Finally, PoCUS can be used in a patient with acute abdominal pain. A hyperdynamic heart with a small and collapsed IVC can point to a ruptured abdominal aortic aneurysm, ectopic pregnancy, or abdominal sepsis. In a patient with pain in the right upper quadrant, PoCUS may display gallstones, cholecystitis, or hydronephrosis. Lower abdominal pain can be caused by urinary retention which can be easily visualized and measured with ultrasound. To adequately interpret the PoCUS results for these clinical conditions, the operator must be aware of the different sensitivities and specificities, as well as the positive and negative predictive values for the individual core applications. These results must be combined with the clinical findings and other results.

4. Training

Each specific core application can be learned in a modular fashion. The IFEM point-of-care ultrasound curriculum guideline provides an overview of the three training steps necessary to learn PoCUS and achieving competency (table 3), namely: initial introduction, gaining experience and achieving competency. This must be complemented with a fourth step which is staying competent.

Table 3. *Steps for training and competency*

Initial introduction	Basic knowledge Specifics of core application Skills development
Gaining experience	Frequent practice for image acquisition and interpretation Practice clinical decision-making, including ultrasound results Awareness of limitations, both technical and operator
Achieving competency	Assessments by trainers
Staying competent	Continuous medical education, peer review

Adapted from IFEM Point-of care ultrasound curriculum guidance[4]

Initial introduction

The initial introduction includes a basic knowledge of ultrasonography, the details of the relevant specific application, and the trainee must demonstrate knowledge and skills under direct trainer supervision. In most countries, a variety of courses are offered, complemented with lectures, demonstrations, readings, E-learning and online teaching videos, local practical sessions, or other sources of information.

Gaining experience

This second phase requires practicing ultrasound on real patients with direct feedback from supervisors,

which may be followed by image review. This can be achieved in the ED or on the ward during morning rounds and key features include: improving image acquisition, interpreting images within clinical context depending on patient characteristics and image quality, and incorporating ultrasound results into clinical decision making. The trainee should demonstrate knowledge about image quality and limitations, in cases of suboptimal images. Image review is possible after the operator-patient encounter and even through remote real-time telemonitored ultrasound (telesonography) during the procedure. Subtle changes, however, in probe handling and movement for improving image quality are best learned hands-on with bedside supervision. Self-learning is sometimes possible if the patient undergoes additional testing, for example, a comprehensive ultrasound or computed tomography (CT) scan. The trainee may ask the patient if he/she can practice performing an ultrasound and compare the results with the results of the CT scan. Most importantly, ultrasound findings must be integrated with other clinical data and test results for optimal decision making. This often is the most difficult part of the PoCUS curriculum and trainees should check their conclusions with colleagues and other specialists. Differential diagnosis of ultrasound findings as well as pitfalls and artefacts are critical and can only be achieved through practice time and ultrasound exposure, feedback, and image review. For example, a multidisciplinary ultrasound meeting can be arranged to discuss interesting ultrasound findings. The trainee should keep track of all ultrasounds performed in a personalised portfolio with documented supervision and the possibility to review images at a later stage (see figure 1 for an example of an ultrasound portfolio with one fictional patient as used in our hospital).

Online learning, gamification, and virtual reality

There are many online ultrasound resources (websites, YouTube tutorials) to assist with learning how to interpret images, especially those that present variations of normal findings and pathological findings. Gamification is more recent learning method, where games or game elements in non-game settings are used, ideally to increase the involvement, focus, learning, or productivity of students.[29] In 2012, The Academy of Emergency Ultrasound organized the SonogGames® at the 2012 Society for Academic Emergency Medicine annual conference, to advance ultrasound education in a novel and interactive way.[30] SonogGames® positively affected medical residents' perceptions and understanding of ultrasound across clinical practice, knowledge and competence, and enthusiasm, and also added new information beyond their completed ultrasound rotations that could be incorporated into clinical practice.[31] Over the past few years, ultrasound games have been developed to assist the acquisition of ultrasound knowledge and to examine skills. These games vary from very simple games such as question-based slot machines (e.g., the Abdominal Ultrasound CME Quiz developed by Philips) or image guessing games (*Can U hear the U-sound?* game developed by the Norwegian University of Science and Technology) to more advanced software with specifically designed probes.[32,33] For example, in an underwater world game, searching for and collecting coins may improve student skills for PoCUS by increasing their spatial orientation and effective probe movements (Underwater: the ultrasound training game, Sfinx Games).[34]

5. Achieving and maintaining competency

The final stage is achieving competency. The trainee must demonstrate competency as assessed by supervisors for three core competencies: image acquisition, image interpretation, and clinical integration/decision-making. It is currently not known how many ultrasounds are needed to qualify as sonographer, and requirements vary, depending on organization. For radiology residents it is known that a minimum of 500 cases is required.[35] ACEP requires at least 25-50 quality-reviewed exams in particular applications but also acknowledges that learning is a lifelong process with improvements beyond training, and that previously-learned psychomotor skills are often needed for new applications. Overall Emergency Ultrasound (EUS) trainees should complete a benchmark of 150-300 total EUS exams depending on the number of applications being utilised.[36] The Dutch Acute Medicine taskforce on sonography organization proposes a minimum of 25 ultrasounds in each application with at least five abnormal findings. However, a recent study showed large individual variation in learning ultrasound technique for the core application IVC and 25 repetitions was inadequate to reach pre-defined competence.[37] In a systematic review, Kanji et al. propose a minimum of five hours of cardiac ultrasound

Figure 1. *Example of a PoCUS portfolio*

PatientID	Patient name	US date	IVC	free fluid	renal/bladder	cardiac	lung	DVT	findings/conclusion	bedside supervision	image review
1234567	Mr.X	20-09-18	1	0	0	1	0	0	IVC > 50% collapse, normal LVEF, no PE, no RV strain	yes Dr.Z	No

The portfolio includes patient data, the ultrasound exams performed, main findings and information about supervision. Abbreviations: US = ultrasound; IVC = inferior vena cava; DVT = deep vein thrombosis; LVEF = left ventricular ejection fraction; PE = pericardial effusion; RV = right ventricle

training with a minimum of 30 scans for binary questions, and reported better outcomes after 15 hours of training.[38]

Entrustable professional activity

It is time to replace the granting of competency based on the completion of a fixed number of ultrasound scans performed with a more competency-based training system. The Entrustable Professional Activity (EPA) concept has competency-based education targets to guarantee that all learners have a sufficient level of proficiency when they reach the required EPA level after training.[39] The competencies should be specific, comprehensive (include knowledge, attitude, and skill), durable, trainable, measurable, related to professional activities, and connected to other competencies.[40] Supervisors of trainees should be able to decide when a trainee may be entrusted to bear the responsibility to perform this professional activity, given the level of competence that is reached. This trust should be earned by demonstrating specific skills and performances with the supervisor present. We suggest an ultrasound EPA model for assessing competence including minimal requirements for each EPA level (table 4).

This model is based on a framework from Schnobrich which shows increasing levels of entrustment ranging from level 1 (not trusted to perform PoCUS even under direct supervision) to level 4 (entrusted to use PoCUS independently).[41] Level 5 is more advanced and includes teaching in ultrasound which may not be reached by many trainees. Using such a model for the evaluation of *every* core application ensures that trainees are able to safely use PoCUS independently after reaching level 4. They are then fully aware of indications and limitations of PoCUS and are able to obtain high-quality images on almost all

Table 4. *EPA levels for PoCUS for each application*

Competence level	Description of competence	Minimal criteria for competence level
Level 1	Is not allowed to use PoCUS on patients - Trainee requires basic ultrasound knowledge and skills (knobology and physiology)	Basic ultrasound course Practice on volunteers Theoretical study
Level 2	Is allowed to use PoCUS with direct supervision - Is able to acquire and interpret basic images with direct feedback or hands-on assistance of supervisor (bedside) - Has basic understanding of indications and pitfalls of PoCUS - Can use PoCUS in simple clinical decision-making	Attends multiple ultrasound training sessions Practice PoCUS under direct supervision with feedback
Level 3	Is allowed to use PoCUS with indirect supervision - Is generally able to acquire high-quality images with correct interpretation - Has more extended knowledge of PoCUS indications and pitfalls, knows when to ask for help/feedback - Can use PoCUS in daily clinical decision-making - Image review by supervisor still required for advanced learning	Has performed and documented at least 10 directly-supervised PoCUS *AND* At least 2 positively rated ultrasound studies by expert (for example with OSATS)
Level 4	Is competent to use PoCUS without supervision - Is able to acquire high-quality images with correct interpretation, even in some difficult cases - Integrates PoCUS fully with clinical decision-making including pearls & pitfalls - Is capable of self-reflection and ongoing learning including PoCUS image review meetings - Is able to supervise trainees for EPA levels 1-3	Has performed and documented at least 25 PoCUS with 25% abnormal findings AND At least four positively rated ultrasound studies by expert (for example with OSATS)
Level 5	Expert in PoCUS - Uses advanced PoCUS applications - Is able to acquire and interpret images in difficult cases - Is involved in local or (inter)national ultrasound educational programs, PoCUS management and implementation issues and/or PoCUS research programs - Active PoCUS education including conference and course visits - Is able to supervise trainees for EPA levels 1-4	Has performed and documented at least 50 PoCUS AND Is engaged in continuous ultrasound educational activities AND Performs PoCUS on a regular basis (several times a week or daily)

Modified from Schnobrich[41]
OSATS = Objective Structured Assessment of Technical Skills

cases. They can also interpret most images and use them for clinical decision-making in conjunction with other clinical findings and have back-up systems for help when needed. There are several ways to demonstrate the specific skills and performances; for example, using specific PoCUS checklists for core applications like the Objective Structured Assessment of Technical Skills (OSATS). Other means of assessing competence can include images or video review with supervision, simulation-based testing including clinical decision-making, and bedside patient assessments with supervision. We have defined a minimal number of normal and abnormal ultrasound exams and OSATS for each EPA level to assist in assessing the trainee and validating the EPA level. Using EPAs with competence and assessment criteria will provide an objective and structured method for assessing PoCUS competence which includes more than becoming competent only based on a fixed number of ultrasound exams performed.

Staying competent

Finally, after achieving competence, an additional step is introduced: every doctor must maintain competency through continuous medical education. Most important is using ultrasound on a regular basis and, if needed, combining this with educational sessions or peer review. In addition to practicing ultrasound, IFEM advises at least 5-10 hours of continuing medical education credits pertaining to ultrasound activities per year.[4]

Quality control

Hospitals and professional organizations (for example the NIV) need to collaborate to make clear guidelines on image archiving, templates for documentation, and medicolegal policies. Images made by internists (including trainees) should also be included in the patient record and accompanied with a clear report about the clinical problem and conclusions. Saved images should be of adequate quality for peer review afterwards. Trainees should have a secured system of updating their personal portfolio with ultrasound images that does not violate privacy regulations.

CONCLUSION

Achieving and maintaining ultrasound competence is a longitudinal experience and these competences can be assessed with EPAs. EPAs are based on a variety of tools and continuous education, rather than absolute numbers of scans. A single course is insufficient to qualify a trainee as a sonographer. A well-designed curriculum is needed. Modern advances, including medical simulation and serious games can have a key role in developing skills and competences. In this article, we have proposed a foundation for an ultrasound curriculum for internists based on the current evidence and guidelines, including judging competency using EPAs.

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ORIGINAL ARTICLE

Familial Mediterranean Fever (FMF): a single centre retrospective study in Amsterdam

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ABSTRACT

Background. Familial Mediterranean Fever (FMF) is the earliest described and most prevalent hereditary auto-inflammatory disease. Its clinical presentation is diverse, leading to possible delay in diagnosis and treatment. Due to immigration, FMF became common in non-Mediterranean European regions. In the present single centre retrospective study, the clinical, demographic, and genetic characteristics of patients with FMF of different ancestry in Amsterdam are described.

Methods. Case records of patients with FMF, who met the Tel-Hashomer diagnostic criteria, were retrospectively analysed. The international disease severity score was used.

Results. Between 1990-2012, 53 patients were identified, 28 were female. Main country of origin was Turkey. The mean age at the time of analysis was 29.1 years; 13.8 years at onset of symptoms; and at time of diagnosis, 22.0 years. Most frequent symptoms were peritonitis (91%) and fever (81%). The mean C-reactive protein and erythrocyte sedimentation rate during acute attacks were 133 mg/l and 37 mm/first hour, respectively. One patient developed amyloidosis as a complication. Seventeen patients underwent abdominal surgery before diagnosis. Most patients (92%) received colchicine treatment and were responsive (81%). Most patients classified their disease as a mild disease (42%). MEFV gene mutation analysis was performed in 46 patients; most patients were compound heterozygotes (n = 17), and the most frequent mutation was M694V (n = 18).

Conclusion. FMF in Amsterdam is diagnosed in relatively young patients and the delay to diagnosis is 8.2 years. Disease manifestations and genetic distribution of our FMF patients are comparable to those in Mediterranean regions, suggesting that ancestry is more important than environment.

KEYWORDS

Autoinflammatory disease, Familial Mediterranean Fever, Tel-Hashomer diagnostic criteria

INTRODUCTION

Familial Mediterranean Fever (FMF) is the earliest described and most prevalent hereditary autoinflammatory disease, first described in 1945.[1,2] It is usually inherited as an autosomal recessive trait, but rare cases of dominant transmission have been described in patients with the M694V mutation. The FMF gene, MEFV, is located on chromosome 16p13.3, coding for the protein pyrin.[3,4] Its clinical presentation may be infrequent in non-Mediterranean countries, leading to delay in diagnosis and treatment. Characteristically, patients suffer from recurrent self-limiting attacks of fever and pain caused by pleuritis, peritonitis, arthritis, or erysipelas-like skin

Table 1. *Clinical diagnostic criteria for the diagnosis of FMF*

Major Criteria
Typical recurrent attacks of fever with synovitis or serositis
AA amyloidosis, without predisposing disease
Good clinical response to colchicine maintenance therapy
Minor Criteria
Recurrent attacks of fever
Erysipelas-like skin lesions
Family history of FMF (first-degree relative)
* The diagnosis of FMF should be considered when a patient of Mediterranean origin meets two major criteria, or one major and two minor criteria.
FMF = Familial Mediterranean Fever

lesions.[5,6] The clinical diagnostic criteria are derived from a study at the Tel-Hashomer Medical Centre in Israel.[7] The diagnosis of FMF should be considered when a patient of Mediterranean origin meets two major criteria, or one major and two minor criteria (table 1).

As the name suggests, FMF is most prevalent in populations originating from the Mediterranean region: Sephardic Jews, Armenians, Arabs, and Turks.[5,8-14] In these populations, the prevalence is estimated at around 100-400 per 100,000 inhabitants. Due to extensive immigration in the 20th century, FMF is also reported in non-Mediterranean regions. For example, Germany, Italia, Czech Republic, and Japan reported patients with this auto-inflammatory disorder.[15-19] Except for few case reports, FMF is not well documented in the Netherlands.[20-23] Approximately 800,000 migrants, originally coming from areas where FMF is endemic, are living in the Netherlands. The majority of them are living in cities such as Amsterdam.[20]
The objective of this retrospective study was to describe FMF patients in Amsterdam, focusing on clinical, demographic, and genetic characteristics in a population of different ancestries. A comparison was made with FMF patients living around both Mediterranean and non-Mediterranean regions based on previous reports.

MATERIALS AND METHODS

Study design

Medical records of 53 patients from 1990 until 2012 in a teaching hospital, Onze Lieve Vrouwe Gasthuis (OLVG)-West in Amsterdam, were retrospectively studied.

Case definition

The inclusion criteria were paediatric or adult patients who met the clinical diagnostic criteria from the Tel-Hashomer study.[7] For each patient, the following clinical, demographic, and genetic characteristics were extracted from the medical record. *Demographic characteristics*: gender, age, country of origin, and consanguinity of parents.

Clinical characteristics: age at onset of symptoms and at diagnosis to calculate time from onset of symptoms to diagnosis; clinical features (fever, peritonitis, arthritis, pleuritis, and/or erysipelas-like skin lesions); laboratory findings during acute attacks (C-reactive protein and erythrocyte sedimentation rate); disease-related complications (proteinuria and/or amyloidosis; proteinuria was measured initially through urine dipstick screening, and 24-hour collection was performed in order to quantify proteinuria); abdominal surgery; response of treatment (measured in use of colchicine related to frequency of attacks before and after use); and disease severity score (table 2).[24,25]

Table 2. *The international severity scoring system for FMF (ISSF)*

	Criteria	Points
1	Chronic sequela (including amyloidosis, growth retardation, anaemia, splenomegaly)	1
2	Organ dysfunction (nephrotic range proteinuria, FMF-related)	1
3	Organ failure (heart, renal, etc, FMF-related)	1
4a*	Frequency of attacks (average number of attacks between 1 and 2 per month)	1
4b*	Frequency of attacks (average number of attacks > 2 per month)	2
5	Increased acute-phase reactants (including C-reactive protein, serum amyloid A, erythrocyte sedimentation rate, fibrinogen) during the attack-free period, ≥ 2 weeks after the last attack (at least two times, 1 month apart)	1
6	Involvement of more than two sites during an individual acute attack (pericarditis, pleuritis, peritonitis, synovitis, ELE, testis involvement, myalgia, etc.)	1
7	More than two different types of attacks during the course of the disease (isolated fever, pericarditis, pleuritis, peritonitis, synovitis, ELE, testis involvement, myalgia, etc.)	1
8	Durations of attacks (more than 72 h in at least three attacks in a year)	1
9	Exertional leg pain (pain following prolonged standings and/or exercising, excluding other causes)	1
Total score		10

Severe disease ≥ 6, intermediate disease = 3-5, mild disease ≤ 2. * Criterion 4a/4b can give 0 or 1 or 2 points altogether according to the definition.
FMF = Familial Mediterranean Fever; ELE = erysipelas-like erythema.

Genetic characteristics: genetic analysis was initially done by screening for known gene mutations in the MEFV gene. Since 2010, mutations in exon 1 until 10, inclusive of intron en exon transitions, were tested. Variants are described as homozygous, heterozygous, or compound heterozygous mutations.

Statistical analysis

Statistical analysis was performed using SPSS 21.0 (SPSS Inc., Chicago, IL). Results are expressed as means ± standard deviation (SD) for continuous variables and frequencies/ rates were measured for discrete variables. Means of the groups were compared with the Student t-test and one-way ANOVA test; a p-value < 0.05 was considered significant. The ethics committee of OLVG-West approved the study. An information letter instructed patients or their parents, in cases of minorities. All of them gave informed consent.

RESULTS

Table 3. *Demographic characteristics of 53 FMF patients in the Netherlands*

	Number of patients	Percentages
Female	28	53
Male	25	47
Mean age (years)	29.1 (14.8 – 43.4)	
Ethnicity		
Turkish	38	72
Arabs	10	18
Syrians	2	4
Armenian	1	2
Iraqi	1	2
Iranian	1	2

FMF = Familial Mediterranean Fever

Demographic characteristics

Demographic characteristics of 53 FMF patients are demonstrated in table 3: 28 patients (53%) were female. Their mean age at the time of analysis was 29.1 years. The main ethnicity was Turkish (n = 38, 72%).

Clinical characteristics

Clinical characteristics are demonstrated in table 4. The mean age at onset of symptoms was 13.8 years. Twenty-three patients (43%) were younger than 10 years at the time of onset of first symptoms, 11 (21%) patients were between 10-19 years, 11 patients (21%) were between 20-29 years, 6 patients (11%) were between 30-39 years, and in 2 (4%) patients, this was unknown. The mean age at diagnosis was 22.0 years and the mean delay to diagnosis was 8.2 years. According to gender, mean age at onset of symptoms was significantly earlier in females (11.6 years) compared to males (16.0 years); p-value 0.000. Mean age at diagnosis was also significantly earlier in females (18.7 years) compared to males (25.1 years); p-value 0.000. However, there was no significant difference in mean time from onset of symptoms to diagnosis between both sexes: 7.1 and 9.1 years, respectively (p-value 0.420).

The main clinical features during acute attacks were abdominal pain reflecting peritonitis (91%) and fever (81%). Less frequent complaints were pain in the hip, knee, or ankle reflecting arthritis (34%), thoracic complaints reflecting pleuritis (34%), or erysipelas-like skin lesions (2%). Most patients had multiple (two or three) clinical features during acute attacks. Forty-nine patients (93%) experienced the same pattern of clinical features during recurrent attacks.

Inflammatory markers were elevated during attacks: the mean C-reactive protein value and erythrocyte sedimentation rate were 133 mg/l and 37 mm/first hour, respectively. One patient who was 20 years at onset of first symptoms and 26 years at diagnosis with a homozygote M694V mutation, had histologically-proven amyloidosis (kidney biopsy) with proteinuria (5.6 g/24h) as a disease-related complication. One other patient had proteinuria (5.4 g/24h) without histological examination. Seventeen (32%) patients underwent abdominal surgery, because there was a suspicion of appendicitis, cholecystitis, or adnexitis and the diagnosis of FMF was not considered. Pathological examination showed no evidence of infectious inflammation in all of these cases.

Most patients used colchicine 0.5mg once or twice a day (n = 15, 31% in both groups). In four patients (8%), no treatment was given, either because the attacks were infrequent (one patient) or because the patients refused treatment (three patients). Before treatment, most patients had multiple monthly attacks (n = 36, 75%). The use of colchicine reduced this frequency; for 28 patients (58%), the attack rate was reduced to several times a year, and for 11 patients (23%) to less than once a year. Nevertheless, nine patients (19%) were unresponsive to colchicine treatment.

Based on the internationally accepted disease severity score for FMF,[23,24] most of the patients classified their disease as mild (n = 22, 42%).

Genetic characteristics

Screening of the MEFV gene for known gene mutations was performed in 46 patients and is demonstrated in table 5. In one patient, no known mutation in the MEFV gene was found and in one patient, a benign heterozygote mutation (G764G) was found. Most patients (n = 17, 39%) were compound heterozygotes, 15 patients (34%) were homozygotes and 12 patients (27%) were

Table 4. *Clinical characteristics in 53 FMF patients in The Netherlands*

Age at FMF onset, diagnosis and delay to diagnosis*		
Mean age at onset of symptoms (years)	13.8 (2.8-24.7)	
Mean age at diagnosis (years)	22.0 (8-35.9)	
Mean time from onset of symptoms to diagnosis (years)	8.2 (5.2-11.2)	
Laboratory values during acute attacks**		
C-reactive protein	133 mg/l (mean ± SD 28-237)	
Erythrocyte sedimentation rate	37 mm (mean ± SD 13-62)	
	Number of patients	**Percentages**
Symptoms during acute attacks*		
Peritonitis	48	91
Fever	43	81
Arthritis	18	34
Pleuritis	18	34
Erysipelas-like skin lesions	1	2
One or multiple symptoms (respectively 1, 2, 3 or 4 symptoms)	7, 22, 19, 5	13, 4, 36, 9
Abdominal surgery		
Yes	17	32.
Appendectomy	10	44
Cholecystectomy	5	22
Adnexectomy	3	13
Other surgery	5	22
One or multiple surgeries (respectively 1, 2 or 3 surgeries)	13, 2, 2	76, 12, 12
Treatment		
Use of colchicine^		
No use	4	8
1 dd 0.5 mg	15	31
2 dd 0.5 mg	15	31
3 dd 0.5 mg	9	19
> 1.5 mg dd	5	11
Frequency of attacks before use of colchicine		
Several times a month	36	75
Several times a year	12	25
Frequency of attacks after use of colchicine		
Several times a month	9	19
Several times a year	28	58
Less than once a year	11	23
Disease severity score#		
Mild disease	22	55
Moderate disease	12	30
Severe disease	6	15

* Missing data from two patients; ** Missing data from 10 patients, ^ Missing data from 5 patients; # Missing data from 13 patients
FMF = Familial Mediterranean Fever; dd = daily dose

heterozygotes. The most frequent gene mutation was M694V which was found in 18 patients in total: in four patients as a homozygotes mutation, in seven patients as a heterozygotes mutation, and in seven patients as a compound heterozygotes mutation.

DISCUSSION

This retrospective study describes the first series of FMF patients in the Netherlands, focusing on clinical, demographic, and genetic characteristics. For early recognition and diagnosis of FMF in the Netherlands it is important to investigate and recognize the clinical presentation of FMF in non-Mediterranean European countries and compare these findings to the previously described spectrum in patients living in the Mediterranean region.

The main ethnicity in our population was Turkish, reflecting previous immigration from Turkey to the Netherlands, with a high estimated prevalence of FMF (1/1000) and high carrier frequency of 20% in the

Table 5. *Genetic characteristics of 44 FMF patients in the Netherlands**

	Number of patients	Percentages
Homozygotes	**15**	**34**
M694V	4	27
M694I	4	27
M680I	5	33
R761H	1	7
E148Q**	1	7
Heterozygotes	**12**	**27**
M694V	7	58
M694I	2	17
M680I	1	8
R761H	2	17
Compound heterozygotes	**17**	**39**
M694V/M680I	5	29
M694V/V726A	1	6
M694V/E148Q**	1	6
M680I/V726A	2	12
M694I/E148Q**	4	24
V726A/R761H	1	6
R408Q**/P369S**	3	18

* Other patients not listed in table 5: n = 7, no screening for MEFV gene mutation performed; n = 1, no known MEFV gene mutation found; n = 1, benign heterozygote mutation found (G764G).
** Mutation of uncertain significance

Turkish population.[13] Some studies have reported a higher prevalence of FMF in males, others reported a similar female/male ratio, similar to our study population.[9,12,14] All of our included patients have ancestors in endemic regions. Despite well-defined clinical diagnostic criteria by Tel-Hashomer, the episodic nature with short recurrent self-limiting attacks of fever and pain makes FMF a diagnostic challenge.[5-8] Because of a low prevalence of FMF in non-Mediterranean regions, we expected a longer period from onset of symptoms to diagnosis in our study, because of the relative unfamiliarity of physicians with FMF. While symptoms of FMF started at a relatively older age than described in Mediterranean studies, we did not find a significantly longer delay of diagnosis. In our patients, symptoms started at a mean age of 13.8 years compared to 9.6 years in Turkish patients and to 67%, 80%, and 64% of the patients diagnosed with FMF before the age of 10 years in Jewish, Arab patients and Armenian patients, respectively.[9,10,13] This finding is in contrast to other case series on FMF patients in non-Mediterranean countries.[17,19] Our study showed similar delay from onset of symptoms to diagnosis compared to the Turkish FMF Study Group; 8.2 years compared to 6.9 years.[13] Mediterranean studies reported delay of diagnosis ranging from 8 to 11 years.[11,14] In other non-Mediterranean studies, there was a longer delay of diagnosis: 14.89 ± 10.10 years (median) in German patients, 18 years (9-27 years) in Italian patients and 9.1 years ± 9.3 years in Japanese patients.[16,17,19]

Clinical symptoms of Dutch FMF patients demonstrate a similar pattern as described in other Mediterranean and non-Mediterranean studies. Peritonitis (63-95%) and fever (78%-100%) are the most frequently described symptoms during acute attacks.[9-11,13,15,17,19] While pleuritis was more frequently seen in non-Mediterranean studies compared to Mediterranean studies (49% vs 40%), arthritis and erysipelas-like skin lesions were more frequently seen in Mediterranean studies compared to non-Mediterranean studies (52% vs 32% and 22% vs 18%). Simliar to other studies, appendectomy and cholecystectomy were the most frequently performed abdominal operations (35% and 11% in Arabs patients and 19% and 2% in Turkish patients, compared to 44% and 23% in our study).[11,13]

Amyloidosis is the most serious complication of FMF, with a prevalence of 14% in non-Mediterranean studies and 13% in Mediterranean studies.[9-11,13,15,17,19] We found a low frequency of amyloidosis: only one patient (2%) suffered from histologically-proven amyloidosis with proteinuria. Similar to previous genetic studies, the patient was homozygote for the M694V mutation, which is associated with a higher prevalence of amyloidosis.[26] A possible explanation for this low incidence of amyloidosis in our study is the fact that colchicine was standard treatment for most FMF patients in our study.

In our study, 92% of the patients were treated with colchicine, which significantly reduced the frequency of attacks. Mediterranean studies reported a higher percentage of patients on colchicine and at a higher dose with better response rates of complete or partial remission ranging from 92% to 97%, compared to 81% in our study.[11-14] Our results are consistent with other non-Mediterranean studies, with response rates ranging from 75 to 92%.[15-17,19] Few studies reported the disease severity score, while in our study, most patients classified their disease as mild (42%); in other non-Mediterranean studies, most patients classified their disease as moderate (63% to 66%).[16,17]

Focusing on the genetic characteristics based on Mediterranean studies, five mutations (V726A, M694V, M694I, M680I, and E148Q) account for approximately 75% of FMF mutations. In our study, these mutations represent 86% of all known mutations. Seventeen patients (39%) were compound heterozygote. The most frequent gene mutation in our study was M694V, similar to both Mediterranean and non-Mediterranean studies. The most mutations we found in our population are classified as pathogenic/likely pathogenic according to the International Study Group for Systemic Autoinflammatory Diseases.[4] The R408Q and P369S mutations are of uncertain significance and it is unclear if the E148Q mutation is a polymorphism or a disease-causing sequence alteration.

Even though MEFV mutations are more frequent in Mediterranean populations, the frequency of MEFV mutations is much higher in our cohort than in the Turkish general population, where M694V and P369S have frequencies of 2.6% (95% CI: 1.6-4.0) and 1.0% (95% CI: 0.5-2.0), respectively.[27] The high yield of pathogenic mutations in suspected MEVF patients warrents genetic screening.

In conclusion, in a population of Dutch FMF patients, all originating from countries with a high FMF prevalence, the age of onset of symptoms and of diagnosis is similar to Mediterranean studies. Disease manifestations and genetic distribution of Dutch FMF patients is also comparable to those in Mediterranean regions. Our results suggest that environmental factors are of little influence on the clinical manifestations in FMF patients. Treating physicians in non-Mediterranean European countries should be aware of FMF in patients with a Mediterranean origin.

DISCLOSURES

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CASE REPORT

Soft tissue infection after photoselective vaporization of the prostate: a life-threating complication

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ABSTRACT

Bladder outlet obstruction is a common aetiology of lower urinary tract symptoms in adult men and several treatment options are available. We report on a case of a 73-year-old man with a complicated soft tissue infection due to an urinoma after laser prostatectomy. He was treated by several surgical interventions and long-term antibiotic therapy.

KEYWORDS

Laser vaporisation, bladder outlet obstruction, soft tissue infection, sepsis

What was known on this topic?
Photoselective vaporisation of the prostate has emerged as a non-inferior invasive treatment option for bladder outlet obstruction causing lower urinary tract symptoms in adult men, in terms of clinical improvement and complication rates.

What does this add?
This report adds that clinicians should be aware of the rare but potential life-threating infectious complication that may occur when using the vaporisation technique rather than the transurethral resection.

INTRODUCTION

Lower urinary tract symptoms are common in adult men, especially with increasing age. Bladder outlet obstruction (BOO) is one of the most prevalent aetiologies, affecting up to 80-90% of men above 70 years of age.[1] Transurethral resection of the prostate (TURP) is considered the surgical therapy of first choice for BOO.[2] In 2002, photoselective vaporisation (PVP) was introduced as a novel technique, using a 532 nm laser light, which is absorbed by haemoglobin leading to vaporisation of prostate tissue. It is preferably used in larger prostate volume and patients using anticoagulation therapy.[3] Common complications are irritative symptoms, urinary retention and urinary tract infection (UTI).[4] Here, we discuss a patient with a rare but serious complication of PVP.

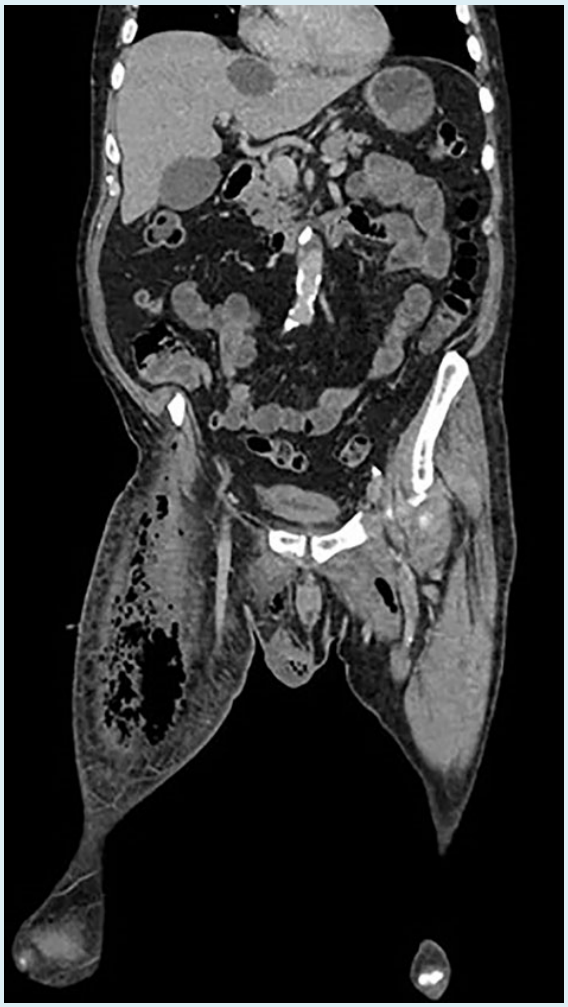
CASE REPORT

A 73-year-old man presented to the emergency department with fever, chills, and pain in his lower abdomen and both legs for the last week. His medical history only comprised recurrent UTIs. Eighteen days before presentation, he underwent a 180-Watt (W) potassium titanyl phosphate laser PVP of the prostate because of BOO with a prostatic volume of 90 millilitres. Preoperative urine culture was positive for *Staphylococcus aureus*, susceptible to cotrimoxazole, which was used preoperatively. Upon presentation, he was unable to stand due to intractable pain. There were no other symptoms, specifically no pain associated with urine voiding.

At physical examination we saw an acutely ill patient with a fever of 39.8 degrees Celsius, a tachycardia of 145 beats per minute, and remarkable erythema of the medial side of the right upper leg without sharp borders, accompanied by oedema and tenderness. To a lesser extent, there also was erythema on the medial side of the left upper leg.

Ancillary investigations showed a sharply elevated C-reactive protein (433 milligrams per litre), leucocytosis (15.1 x 10^9 per litre) and normocytic anaemia. Renal

Figure 1. *CT scan revealing multiple collections of air in the right upper thigh*



function was impaired. There were no signs of urinary retention as tested with a bladder scan.
Cefuroxime was started and switched to flucloxacillin after blood and urine cultures both became positive for *Staphylococcus aureus*.

Because of persisting fever and extremely painful progression of swelling despite antibiotic therapy, a computed tomography scan was performed, showing multiple gas collections in the subcutis and muscles of the right upper leg, as well as in the abdominal wall, the left medial upper leg, and the scrotum (figure 1), which did not merge with the prostate. Nor were there clear signs of osteitis pubis. The patient was admitted to the intensive care unit after an emergency fasciotomy with drainage of a large volume of pus from different pockets in both legs. There was no tissue necrosis. New collections of pus were drained in several re-explorations. Transoesophageal echocardiography ruled out endocarditis as a possible dissemination of *Staphylococcus aureus* bacteraemia. Repeat blood cultures eight days after admission were negative. Considering that the fever started one week before presentation, a bacteraemia duration of 15 days can be assumed.
A postoperatively-placed vacuum assisted closure system elicited leakage of clear fluid from the right groin with a high concentration of creatinine, consistent with urine. Thus, a prostatic fistula leading to an urinoma was thought to be the underlying cause of his soft tissue infection, despite the lack of a visible fistula on cystoscopic evaluation. Leakage continued after placement of a transurethral and suprapubic urine catheter, causing a new abscess in the right upper thigh, necessitating insertion of a bilateral nephrostomy drain in order to divert urine away from the bladder. The fasciotomy incisions were eventually closed and a subcutaneous drain was left behind. Intravenous antibiotics were continued.
The clinical course was further complicated by two readmissions to the intensive care unit because of persistent respiratory failure due to aspiration pneumonia secondary to ventilation-associated vocal cord paresis. The patient was also in need of temporary continuous renal replacement therapy because of acute kidney failure due to sepsis.
The nephrostomy drains were removed after five weeks to restart urine flow through the transurethral and suprapubic catheters. There was no new leakage of urine through the wounds of the right upper thigh and the transurethral catheter was removed.
After an admission of 113 days, the patient was discharged to a nursing home for intensive rehabilitation and speech therapy. Finally, the suprapubic catheter was removed in the out-patient setting on day 139 after his original admission.

DISCUSSION

Recent literature demonstrated that PVP was associated with faster removal of urinary catheter and shorter hospital admission, whereas other complications rates were similar for TURP and PVP.[5] Compared to TURP, greater reduction of prostatic volume can be achieved with PVP, hence making the latter a better choice for BOO with a larger prostatic volume. Post-procedural UTIs are merely caused by Gram-negative bacteria (75%), mostly *E. coli*.[6] Single-dose preoperative antibiotic prophylaxis results in reduction of bacteriuria, UTIs and bacteraemia.[7] A three-day antibiotic regime can possibly further reduce this risk and a trial is currently being conducted to assess this potential benefit.[8] A less common complication of PVP includes capsular perforation, ranging from 1% to 9% with

increasing power from 80 W to 180 W,[9] compared to 4.0% with TURP.[10,11] Use of 180-W laser is restricted to large bilateral adenoma and is discouraged close to the bladder neck and in the ventral prostate because of increased tissue vulnerability and close vicinity to the os pubis.[12] The complication presented here is most likely due to such perforation, which expanded secondary to local prostatic infection and soft tissue infection of the right upper thigh with *S. aureus* bacteraemia. One case series reported eight patients with prostatic fistula presenting with antalgic gait due to pain in the urogenital region; osteitis pubis was diagnosed in three patients.[13] Another case series reported three cases of osteomyelitis pubis with positive cultures of the bone.[14] One case report described a patient with bilateral thigh urinomas due to prostatic fistula after PVP, similar to the present case.[15] Although PVP has been proven non-inferior to TURP in patients with BOO, we presented a very rare but serious and life-threating infectious complication that urologists and infectious diseases specialists should be aware of.

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CASE REPORT

Cardiac arrest following chloroquine overdose treated with bicarbonate and lipid emulsion

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ABSTRACT

We describe a 27-year-old female with repeated episodes of pulseless electrical activity due to intoxication with a substance that was unidentified at presentation. Severe QRS widening was observed and empiric treatment with sodium bicarbonate and intravenous lipid emulsion was administered.
In this case, intraosseous administration of lipid emulsion failed to improve haemodynamic parameters, suggesting that this dose remained in the bone marrow compartment. We recommend that physicians become aware of this possibility and to avoid intraosseous administration of lipid emulsion.

What was known on this topic?
Empiric treatment based on signs and symptoms is necessary for intoxications with an unidentified substance.
Known chloroquine overdose is treated with early mechanical ventilation, and a high dose of diazepam and vasopressor agents.

What does this add?
Haemodynamic stabilization in chloroquine overdose can be achieved with administration of sodium bicarbonate and intravenous lipid emulsion. Intraosseous administration of lipid emulsion might be less effective.

KEYWORDS

Chloroquine, poisoning, intravenous lipid emulsion, intraosseous, alkalinisation, sodium bicarbonate, diazepam

INTRODUCTION

In Western countries, prescription drugs are used in about 90% of suicide attempts with drugs.[1] In some countries, chloroquine is used in suicide attempts.[2] Chloroquine has a strong membrane-stabilising effect and intoxication may present with neurological, cardiovascular, respiratory, and digestive symptoms. We describe a patient with haemodynamic stabilisation after empiric treatment for intoxication with QRS widening, which turned out to be due to chloroquine. Intraosseous administration of lipid emulsion failed to improve haemodynamic parameters in this case.

CASE REPORT

At home, a 27-year-old female called the emergency number and reported a suicide attempt with medication. Prescribed medicines were clonidin, dextroamphetamine, flurazepam, and promethazine. A few hours after admission, her family reported that she frequently bought medicines online. Upon arrival of the paramedics, she was fully conscious with normal vital signs. While entering the ambulance she became asystolic and cardiopulmonary resuscitation (CPR) was performed for 19 minutes. She was intubated on the scene.
Upon arrival in the emergency department, very broad QRS complexes (326 ms) were observed. An overdose with her prescribed medicines would not cause QRS widening and aside from flumazenil for flurazepam, no specific antidotes are available. Because of the combination of an unknown intoxication and widened

QRS complexes, sodium bicarbonate 100 ml 8.4% and intravenous lipid emulsion (ILE) 20% (100 ml bolus followed by 400 ml infusion) were given via intraosseous infusion. Shortly after arrival, she lost circulation and CPR was restarted according to protocol with addition of intraosseous 950 mg calciumgluconate. The possibility of extracorporal life support was considered, but due to distance and time to start of perfusion, this seemed impossible.

Despite the therapy mentioned above and the start of vasopressors, circulation remained unstable and the patient experienced a total of three cardiac arrest episodes in the hospital due to pulseless electrical activity. As further alkalinisation would aggravate an already very severe hypokalaemia (1.5 mmol/l; reference: 3.5-5 mmol/l), we decided to repeat the full dose of lipid emulsion intravenously as a last possible resort (cumulative dose of 15 ml/kg). Shortly thereafter, haemodynamic parameters and cardiac contractility improved. Toxicological analysis showed a high level of chloroquine (16.1 mg/l three hours after ingestion; reference for toxic level: > 0.5 mg/l) and a positive blood test for benzodiazepines. High-dose diazepam was added, resulting in further improvement of cardiac contractility and the possibility to cease vasopressor agents. Alkalinisation was restarted as soon as potassium stabilised with supplementation; active charcoal was administered repeatedly (total dose of 150 g). After 60 hours, cardiac conduction normalised and therapy with sodium bicarbonate and diazepam was discontinued. Figure 1 shows the timeline of events after ingestion of the overdose of chloroquine. On day seven, the patient was extubated. She made a full recovery from the post-anoxic and toxic encephalopathy.

DISCUSSION

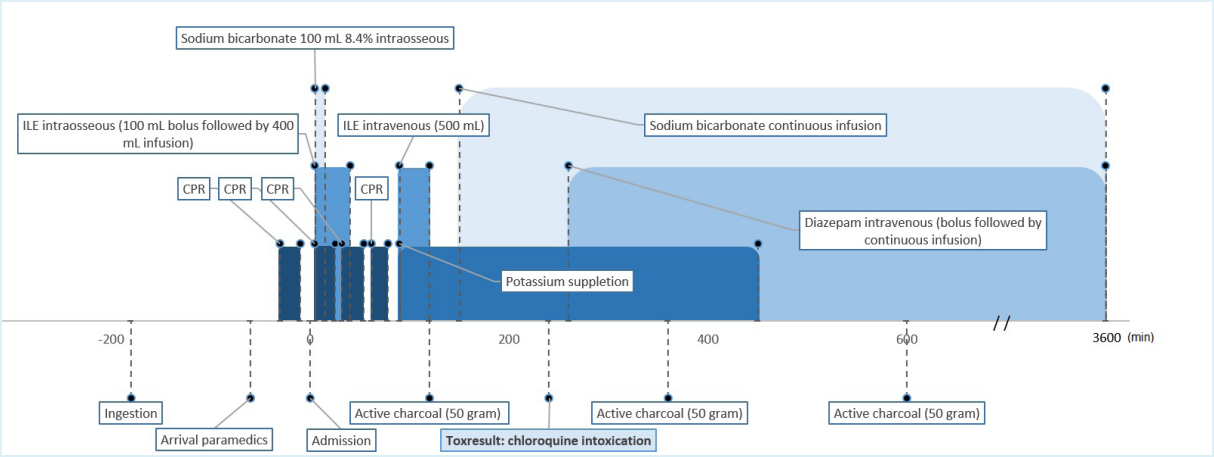
In the Netherlands, chloroquine is rarely prescribed and is unavailable over the counter. In this case, chloroquine was ordered via an internet pharmacy with the intention to commit suicide.

Since the study of Riou et al,[3] patients with chloroquine intoxication are almost always treated with early mechanical ventilation, and a high dose of diazepam and (nor)epinephrine.[2] Although definitive evidence for effectiveness of this approach is lacking, we followed this regimen in our patient. Furthermore, we administered active charcoal since chloroquine is a carbon-absorbable molecule.[4]

Because the ingested substance was initially unknown, we started treatment with sodium bicarbonate because of a widened QRS complex. Sodium bicarbonate is widely used to treat toxin-induced sodium channel blockade, as alkalinisation leads to increased protein binding of the sodium channel-blocking drug. Data of its use in chloroquine poisoning are limited. Since the focus has been on the therapy described above, sodium bicarbonate administration alone is never tested for its efficacy. The most important complication of sodium bicarbonate is hypokalaemia due to intracellular shifting. This is of utmost importance in chloroquine overdose, since one of the features of severe chloroquine intoxication is hypokalaemia, as was the case in our patient.[5,6]

Chloroquine is a highly lipophilic substance; thus, administration of lipid emulsion in case of life-threatening symptoms seems rational. There is little evidence supporting the use of intravenous lipid emulsion (ILE) in (hydroxy)chloroquine intoxications. One report

Figure 1. *Timeline of events after ingestion*



CPR = cardiopulmonary resuscitation; ILE = intravenous lipid emulsion

presents temporary return of spontaneous circulation in cardiac arrest due to chloroquine poisoning after administering ILE 20% (1.5 ml/kg bolus followed by 0.25 ml/kg/min infusion) in one patient.[7] Two other patients were successfully treated with the same dosing regimen of ILE within two hours after suicide attempts with hydroxychloroquine. Both patients were concurrently treated with sodium bicarbonate and diazepam, and vasopressor agents were used in one of them.[8] However, two cases without benefit of ILE were also reported in literature. In the first case, infusion of ILE was started 11 hours after ingestion, in the second case, the ingested dose of hydroxychloroquine was extremely high.[9]

Very few data about intraosseous administration of lipid emulsion exist. An animal study did not show any difference in time to recovery of haemodynamic variables after intravenous bupivacaine injection in rats treated with intraosseous lipid emulsion versus intravenous administration.[10] Sampson and Bedy[11] describe a patient with massive verapamil overdose who received part of the lipid emulsion through an intraosseous line. Administration was limited due to a flow alarm after 60 ml and by that time, intravenous access was established so therapy was moved to that site. The patient died two days after admission. There is one description of successful treatment of seizures after intraosseous injection of lidocaine with intraosseous lipid emulsion in an 11-month-old male.[12]

In the case, we describe that the first dose of ILE was given intraosseous infusion and did not achieve any haemodynamic improvement. Since haemodynamic parameters stabilised and cardiac contractility improved after a second, intravenous dose, we hypothesise that the first dose remained in the bone marrow compartment. There was no flow alarm during infusion of the intraosseous dose and, since we monitored pulsatile output on the catheter in the radial artery and a normal pulse oximetry plethysmographic waveform was seen during CPR, lack of efficiency due to low output does not seem to be the explanation either. Although we cannot exclude the possibility that the first intraosseous dose of lipid emulsion was too low to bind a substantial part of the chloroquine, we recommend that physicians be aware of the possibility that intraosseous lipid emulsion might be less effective and to avoid intraosseous administration of lipid emulsion. Further research on the pharmacokinetics of intraosseous administration of lipid emulsion is necessary.

CONCLUSION

We were challenged with a severe intoxication with chloroquine that was bought online. Successful treatment with sodium bicarbonate and ILE was started before the substance was identified. In our patient intraosseous administration of lipid emulsion was ineffective, compared to intravenous administration.

DISCLOSURES

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

This case was previously presented as a poster presentation at the 38th congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) held in Bucharest (May 22-25th, 2018).

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CASE REPORT

Renal failure, shock, and loss of pacemaker capture: A case of flecainide intoxication

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ABSTRACT

Flecainide intoxication is a severe intoxication that can lead to cardiogenic shock. We report on a 68-year-old female patient, who presented with a flecainide intoxication in the setting of renal failure. She was managed with invasive supportive therapy at the ICU and infusion of sodium bicarbonate and intravenous lipid emulsion (ILE, intralipid 20%), after which she made a complete recovery.

KEYWORDS

Cardiogenic shock, flecainide intoxication, intralipid, intravenous lipid emulsion, sodium bicarbonate.

INTRODUCTION

Flecainide acetate (Tambocor) is a Vaughn-Williams class 1C anti arrhythmic drug and a sodium and potassium channel blocker, mainly used for the treatment of supraventricular arrhythmias but also for ventricular dysrhythmias.[1,2] The therapeutic window for flecainide is narrow and 80-90% of it is eliminated (of which 25-40% is unchanged) by the kidneys.[3] Severe intoxication is associated with a mortality rate of approximately 10%.[4] Here, we present a patient with a severe flecainide intoxication on a background of kidney impairment, who was admitted at the Intensive Care Unit (ICU) and successfully managed with the infusion of sodium bicarbonate and intravenous lipid emulsion (ILE). This case illustrates the importance of prompt symptom recognition and the recognition of medication as the cause of a collapse, especially in the case of kidney dysfunction. Furthermore, it highlights the importance of accurate comparison of new and old ECGs.

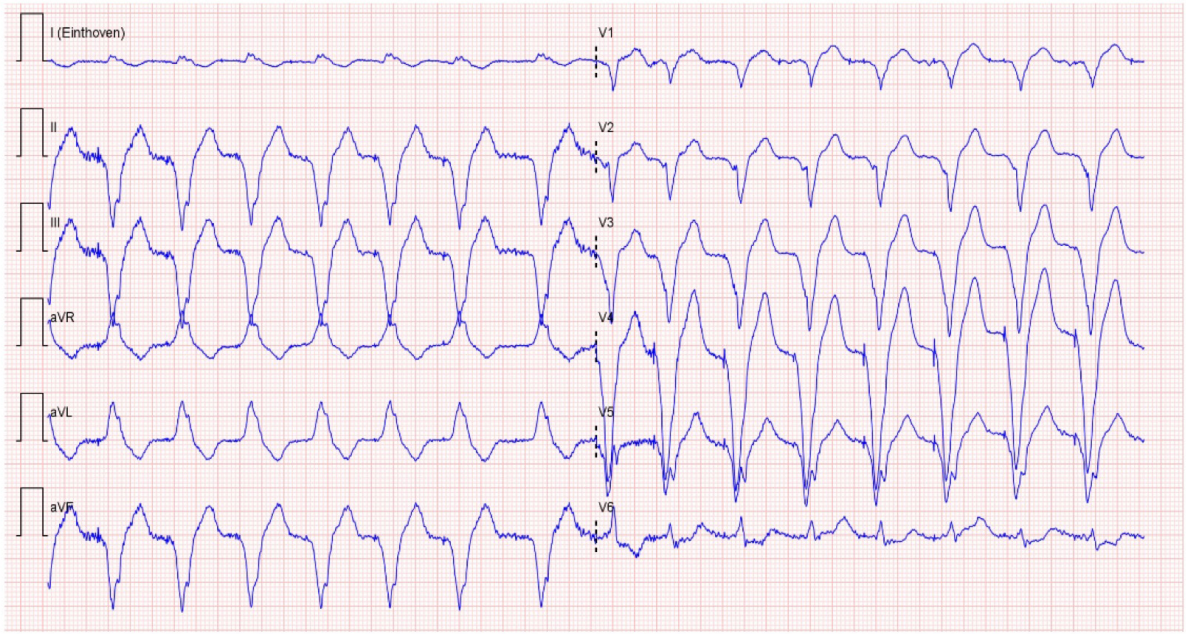
What was known on this topic?
Flecainide intoxication is a severe intoxication which can rapidly lead to various arrhythmias and is associated with high mortality. Flecainide is mainly renally excreted and in case of kidney impairment, the drug can rapidly accumulate. The mainstay of treatment is sodium bicarbonate; newer therapies such as intravenous lipid emulsion have rarely been reported on.

What does this add?
This case report highlights the importance of medication review in the case of renal impairment and the comparison of new and old electrocardiograms (ECG) in case of unexplained collapse. Furthermore, it emphasizes that in patients with severe flecainide intoxication, resulting in cardiogenic shock refractory to standard treatment, infusion of intravenous lipid emulsion should be considered as an adjunctive therapy.

CASE REPORT

A 68-year-old female patient with a medical history of a sick sinus syndrome, for which a dual-chamber, rate-modulated pacemaker was implanted, atrial fibrillation, and chronic renal failure, presented to the emergency department after collapsing. Her home medication consisted of bisoprolol, bumetanide, flecainide and rivaroxaban. Except for bumetanide, this medication was continued at admission.
An old ECG is shown in figure 1 and the ECG at the time of admission to the emergency department is shown in figure 2. Ischemia was ruled out since troponin was negative and a recently performed coronary angiography

Figure 1. *Electrocardiogram approximately one year before admission to the emergency department*



was normal. Her pacemaker report did not reveal arrhythmias. A urinary tract infection was diagnosed and further lab results revealed acute on chronic kidney failure, with a glomerular filtration rate (GFR) declining from 20 to 12 ml/min/1.73m^2 and a creatinine rise from 219 to 318 µmol/l. Thus, intravascular fluid depletion due to the infection was deemed to be the cause of her collapse.

Several days later, she deteriorated with hypotension (inter-beat (RR) interval 80/45 mmHg), bradycardia (heart

Figure 2. *Electrocardiogram at admission to the emergency department*

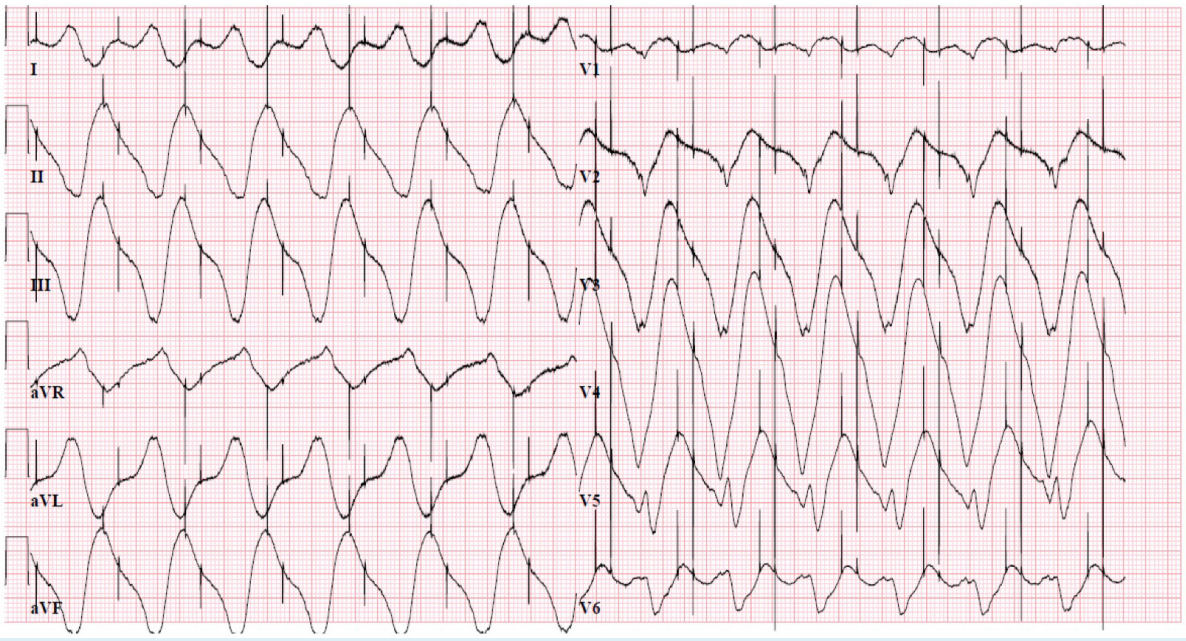
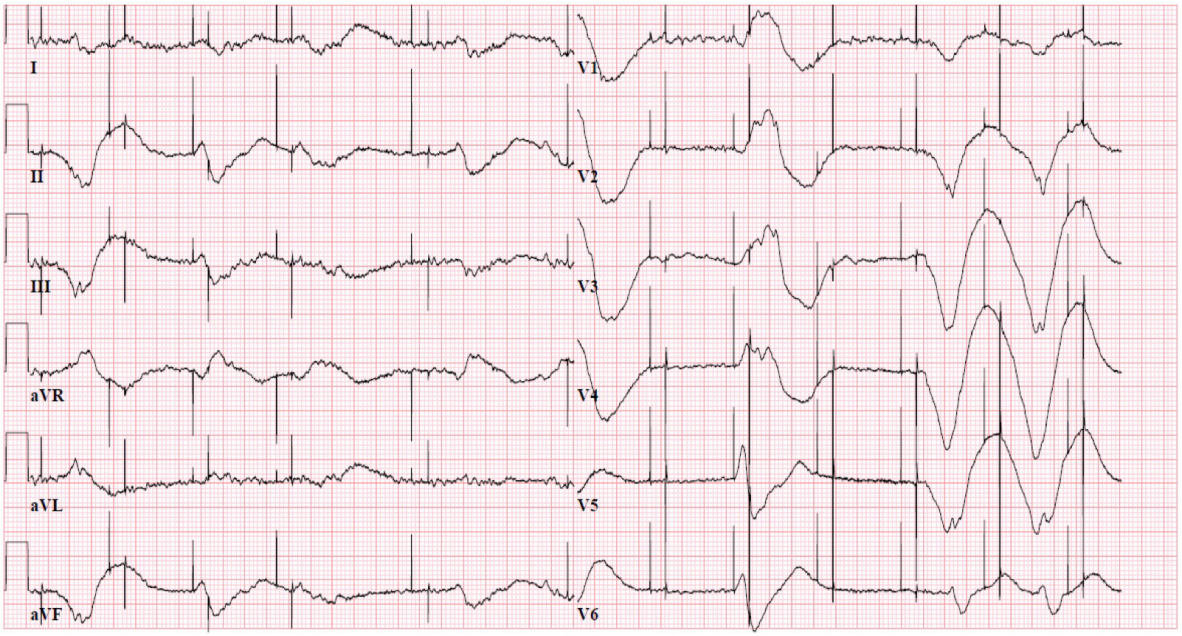


Figure 3. *Electrocardiogram at admission to the Intensive Care Unit*



rate 45-50/min), somnolence, peripheral cyanosis and mottled extremities. She was admitted to intensive care. Further work up revealed:

- Creatinine 530 µmol/l;
- GFR 9 ml/min/1.73m²;
- Arterial blood gas analysis showed a respiratory compensated metabolic acidosis: pH 7.30, pCO_2 2.7 kPa, bicarbonate 9.1 mmol/l, lactate 8.5 mmol/l.

A new ECG (figure 3) demonstrated extreme broad QRS complexes and loss of pacemaker capture. A review of her medication showed that flecainide 200 mg had been continuously administered throughout her admission. We concluded that she was suffering from cardiogenic shock thought to be caused by flecainide toxicity. A flecainide level was obtained, which was indeed within the toxic range: 2.44 mg/l. Although deemed less likely, since our patient was only treated with a very low dose of bisoprolol (2.5 mg once daily) whilst in the coronary care unit (CCU), the contribution of bisoprolol toxicity to the symptoms described above could not be completely ruled out. For this reason, we also obtained bisoprolol levels, which were 0.10 mg/l at ICU admission and non-detectable the day after. Thus, we decided to consider the case as a mono-intoxication with flecainide.

The patient was treated with sodium bicarbonate infusion and intubated shortly after ICU admission because of respiratory exhaustion. She remained anuric and was started on continuous venovenous haemofiltration (CVVH). Despite further supportive treatment with noradrenaline, isoprenaline and dobutamine, hypotension and bradycardia persisted and pulse contour cardiac output measurements remained consistent with low cardiac output (cardiac index 1.4, extravascular lung water index 17.6, global end-diastolic volume index 756). Finally, intralipid 20% was administered at the maximum dosage, resulting in a gradual overall improvement. After 10 days, she was extubated and after 12 days discharged to the CCU.

DISCUSSION

This case report describes a patient who developed a flecainide intoxication, a rare but often fatal intoxication, because of continuous administration of the drug despite declining kidney function.

Flecainide's main effects are exerted through its high affinity for open-state sodium channels, thereby prolonging the depolarisation of myocardial cells. This results in a reduction of cardiac excitability in all parts of the heart.[1,2] The majority of flecainide is renally excreted, 80-90%, of which 25-40% unchanged, with a half-life of approximately 20 hours. At higher doses, flecainide demonstrates non-linear pharmacokinetics, which means elimination half-life increases at higher plasma levels. In severe kidney failure, elimination can be extended to as long as 58 hours and the drug can rapidly accumulate. The normal therapeutic range is 0.2 to 1 mcg/ml, although adverse effects have been reported with plasma levels > 0.7 mcg/ml.[5,6] Our patient's flecainide dose was not

adjusted to her kidney function and flecainide levels were not monitored. This case report highlights the importance of medication review in case of kidney failure.

The clinical features of flecainide toxicity vary from blurred vision to hypotension and bradyarrhythmias as well as tachyarrhythmias. Severe intoxication can be fatal: the mortality rate of flecainide intoxication has been estimated at 10%.[4,7] The electrophysiologic properties of flecainide are manifested on ECGs as PR and QTc interval prolongation and QRS widening.[8,9] When the QRS interval is widened more than 25% compared to baseline, this is considered as the threshold for dose reduction or discontinuation of the drug. When the QRS duration is increased by 50% or the PR interval is prolonged by 30%, toxicity should be suspected.[8,10] In hindsight, when comparing ECG 1 and 2, we can conclude that QRS complexes were already profoundly wider at admission to the emergency department. This should have prompted the treating clinicians to consider flecainide as the cause of her collapse and reduce the dosage or discontinue the drug.

Since flecainide intoxication is rare, literature on treatment options is limited.[7] In addition to ICU admission for invasive supportive management and correcting aggravating conditions for arrhythmias, such as hypoxia and electrolyte disturbances, high-dose sodium bicarbonate infusion is the cornerstone of treatment. It acts by antagonizing flecainide at its binding site to sodium channels on cardiac myocytes. Aggressive treatment is required and doses up to 350 mEq have been reported to maintain a goal pH of 7.45-7.55.[6,11] Because of the refractory state of the cardiogenic shock in this patient, ILE was also administered. This is a novel strategy and has only been described in a few case reports.[12-14] The mechanism of action is not completely understood, but various potential mechanisms have been proposed. The most prevalent is the 'lipid sink' theory, suggesting that with lipid administration, the intravascular lipid phase is expanded, which extracts the offending lipid soluble drug from its target tissue. Another hypothesis theorises that lipid administration serves as a myocardial energy substrate, thereby improving cardiac function.[15] Our patient was successfully managed with ILE and we think it should be considered as adjunctive therapy in patients with refractory cardiogenic shock secondary to flecainide overdose.

DISCLOSURES

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

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PHOTO QUIZ

An unusual cause of fever and cytopenia in multiple myeloma

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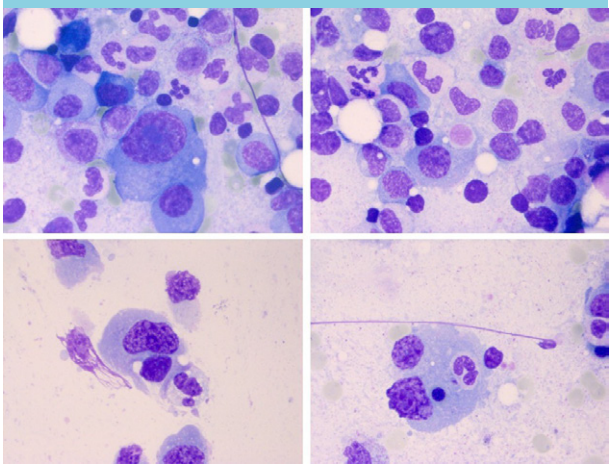
Figure 1. *Bone marrow aspirate showing neoplastic plasma cells*



CASE REPORT

A 79-year-old man was admitted to the hospital complaining of fever for the past two weeks and cold shivers for the past one day. His medical history included multiple myeloma for which he was treated at that time with melphalan, prednisolone and bortezomib, as fourth line chemotherapy.

According to the patient, he had no localizing complaints that indicate a focus of infection. Standard clinical evaluation did not reveal a site of infection. Laboratory results showed elevated inflammation parameters (C-reactive protein 186 mg/l) and a cytopenia (haemoglobin 7.8 gl/dl, mean corpuscular volume 99 fl, leukocyte count 4.2 x10^9/l, thrombocyte count 148 x10^9/l). Blood cultures, virus serology (Epstein-Barr virus, cytomegalovirus and herpes simplex virus) and imaging with computed tomorography, positron emission tomography-computed tomography and echocardiography revealed no focus of infection. Fever and cold shivers persisted despite broad spectrum antibiotics. Since the pancytopenia worsened despite a decrease of the Immunoglobin A lambda paraprotein level, a bone marrow puncture was performed.

WHAT IS YOUR DIAGNOSIS?

See page 194 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 193)

AN UNUSUAL CAUSE OF FEVER AND CYTOPENIA IN MULTIPLE MYELOMA

DIAGNOSIS

The bone marrow examination showed 20% atypical plasma cells with haemophagocytosis of erythrocytes and leukocytes by these plasma cells (figure 1). The atypical plasma cells expressed CD138 and showed lambda monoclonality. Acquired haemophagocytosis or hemophagocytic lymphohistiocytosis (HLH) is usually characterized by haemophagocytosis by histiocytes and mostly associated with (viral) infections and haematologic malignancies, including (rarely) multiple myeloma. The pathogenesis of HLH is not fully elucidated but characterized by increased production of pro-inflammatory cytokines and activation of cytotoxic T cells and macrophages, reflected by increased serum levels of soluble Interleukin-2 receptor and ferritin, respectively.[1] Haemophagocytosis by neoplastic plasma cells, as seen in our case, is extremely rare and only a few reports describe phagocytic plasma cells in patients with multiple myeloma or plasma cell leukaemia.[2-5] Normal plasma cells are immunoglobulin-producing cells and do not have the ability to phagocytise. The mechanism of acquisition of phagocytic capacity by malignant plasma cells is unclear. Malignant plasma cells isolated from the bone marrow of one of the reported patients revealed no *in vitro* phagocytic capacity.[2] The occurrence of haemophagocytosis is not related to a specific immunoglobulin or light chain subtypes,[3] but occasionally associated with aberrant immunophenotypic (CD15+) features.[4] Haemophagocytosis by plasma cell seems more frequently in female patients and it appears that mature erythrocytes and platelets are predominantly phagocytised. The pathophysiological mechanism of myeloma-mediated haemophagocytosis is different from that of the HLH. Thus, the normally-associated biochemical clues, such as a strongly elevated ferritin level, directing the diagnosis of haemophagocytosis as cause of the pancytopenia may not be present. Response to treatment has only been reported in nine patients, of which six showed clinical improvement.[3] In our case, treatment with high-dose dexamethasone was started, and within days, the fever and cold shivers disappeared and the patient felt better. However, he refrained intensive chemotherapeutic treatment and died a few weeks later.

DISCLOSURES

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

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LETTER TO EDITOR

Yellow nail syndrome: differentials and prognosis

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We read with much pleasure the article 'Yellow nail syndrome with complete triad' by Kuwahara et al., published in *The Netherlands Journal of Medicine*. The authors have done an excellent job in describing a patient with yellow nails, non-pitting leg edema and bilateral pleural effusions in the background of diffuse parenchymal micronodules.[1] The authors have tried to rule out various conditions including onychomycosis, tuberculosis, cardiac failure, renal failure, liver failure, hypothyroidism; and exposure to medications such as bucillamine and D-penicillamine. The reader needs to be aware that various underlying systemic diseases like connective tissue disease, malignancies, endocrine abnormalities, and immunodeficiency states can present with yellow nail. In fact, the most common connective tissue disease presenting with yellow nail syndrome (YNS) is reported to be rheumatoid arthritis.[2] Did the patient give a past history of rheumatoid arthritis? Knowing this is important, as patients with past history of rheumatoid arthritis treated with older disease-modifying agents such as gold, penicillamine, and bucillamine can present with YNS.[2] Even though many of these conditions can mimic yellow nail, the rate of nail growth in patients with a yellow nail syndrome is very slow compared to normal nail growth. Similarly, the triad of clinical manifestations of YNS is variable over time, and hence the presence of any two of three manifestations in the absence of other contributory cause could prompt the diagnosis of YNS. The authors have appropriately ruled out the presence of heart failure, and it is also prudent to rule out fungal infection of the nail with the help of microscopic visualization and fungal culture of the nail.

We would also like to add that yellow nail, being the most common presentation of YNS, has been reported to be successfully treated with vitamin E, zinc, the azole group of antifungals, and intralesional triamcinolone.[3] YNS secondary to drug treatment, have been reported to improve following withdrawal of offending agents. Pleural effusions have been treated with pleurodesis as mentioned by the authors. The median survival of patients with YNS has been reported to be 132 months, (11 years) and we beg to defer from the authors regarding its prognosis as being poor.[3]

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Response

Dear Dr. Paul van Daele, *Editor-in-Chief,*
Dear Dr. Mishra and colleagues,

Thank you for your constructive suggestions. As the authors described in 'Letter to Editor', the most important consideration when diagnosing yellow nail syndrome (YNS) is to rule out other possibilities that cause yellow-coloured nails. In our case, the patient did not have any symptoms which indicates connective tissue disease and had no past medical history of rheumatoid arthritis. His serological tumour markers were also

negative and multiple cytopathologic examinations of pleural fluid showed no malignancy. The rate of nail growth is also useful to diagnose YNS, since nail growth rate among patients with YNS is very slow compared to other differential diagnoses of yellow nails such as tinea unguium, pachyonychia, tetracycline, and hypothyroidism.[1] We agree with the authors that biopsies from his nails may rule out fungal infections, however, we failed to obtain his consent for such testing. As an alternative, we started antifungal agents, but the discoloration of his nail did not alter.

The authors also provided important insight into the treatment for YNS. We agree that several reports stated that vitamin E, clarithromycin, and azole antifungals were effective for the treatment of yellow nails accompanied with YNS, and that clarithromycin, in particular, may reduce lymphoedema and promote nail growth;[2] however, it is also true that a well-established treatment strategy still does not exist. But we do agree that consideration of these medications may reduce symptoms and lead to a true diagnosis.

The authors described prognosis of YNS on the basis of same references we cited, but we still believe that median diagnosed age of 61 years with median survival length of 132 months is still not enough to be considered long-term.[3] We appreciate the time and effort Dr. Mishra and colleagues have dedicated to provide us with insightful feedback on ways to strengthen our manuscript and to advance medicine for rare disorders.

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