Volume 31, Issue 2, 2019

Malta Medical Journal

University of Malta
Medical School

L-Università
ta' Malta

www.mmsjournals.org

Table of Contents

Towards evidence-based medical cannabis

Victor Grech

Abstract

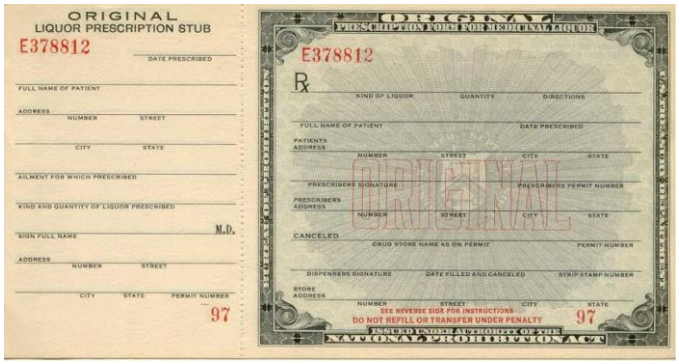
Medical cannabis (MC) is at a crossroads. The MC industry needs evidence-based medicine to sell MC as there is still some residual stigma among the medical profession. Furthermore, evidence is needed in order to persuade doctors to prescribe. The requisite papers must be high quality research: double-blind, randomized control trials, systematic reviews and meta-analyses. As it is, MC currently incorporates relatively few commercial products, and those that are developed and marketed with standardized ingredients and with the requisite quality control (e.g. nabilone) have been welcomed by the medical community as they permit proper trials. At the time of writing, evidence for the usefulness of MC is limited and MC is associated with significant side effects. Clearly, new products and more clinical trials are required. Product development and trialing will take time and will cost money. There is a knowledge gap that must be bridged if MC is to ever be treated as medicine and routinely prescribed. MC must meet the same exacting standards of quality, effectiveness and safety of any other prescription drug or it risks being ignored or marginalized by the medical community. For all of these reasons, including the many unanswered questions, the MC industry constitutes an exciting and lucrative opportunity for Malta.

Victor Grech PhD (London), PhD (Malta), FRCPCH, FRCP(UK), DCH
Department of Paediatrics
Mater Dei Hospital
Msida
victor.e.grech@gov.mt

Introduction

Medical cannabis (MC) is at a crossroads just like alcohol during prohibition from 1919 in the United States after the 18th Amendment which banned access to alcohol. Indeed, alcohol was a prescription item, which could be prescribed by doctors for specific indications (figure 1).[1]

***Figure 1**: Prohibition era medicinal alcohol prescription*



Medical Cannabis

Cannabis is a complex set of compounds (circa 400–500) which include cannabinoids, terpenes and flavonoids. These interact and produce the so-called entourage effect[2] whereby non-psychoactive compounds (mostly cannabidiol - CBD) modulate the psychoactive effects of (mostly) THC (tetrahydrocannabinol).

The MC industry needs evidence-based medicine to sell MC as there is still some residual stigma among the medical profession and evidence is need in order to persuade doctors to prescribe after interacting with medical representative and after exposure to studies in conferences.

The requisite papers must be high quality research: double-blind, randomized control trials (RCT), systematic reviews and meta-analyses. For example, in the UK, the study hierarchy for evidence based medicine is as per table 1.

Table 1: *Evidence-based medicine: study hierarchy, UK (abridged)*

1a:	Systematic reviews of randomized controlled trials.
1b:	Individual randomized controlled trials.
2a:	Systematic reviews of cohort studies.
2b:	Individual cohort study/low quality RCT.
3a:	Systematic review of case-control studies.
3b:	Individual case-control study.
4:	Case series.
5:	Expert opinion.

The medical profession expects level 1 evidence. Such evidence would further promote MC with the inevitable inclusion in guidelines. For example, the European Societẏs guidelines for the treatment of hypertension are based on, and literally riddled by levels of evidence (figure 2).[2]

Figure 2: *European Society's guidelines for the treatment of hypertension – see levels of evidence and class thereof on the right.*[2]

Drug treatment strategy for hypertension

Recommendations	Class[a]	Level[b]
Among all antihypertensive drugs, ACE inhibitors, ARBs, beta-blockers, CCBs, and diuretics (thiazides and thiazide-like drugs such as chlorthalidone and indapamide) have demonstrated effective reduction of BP and CV events in RCTs, and thus are indicated as the basis of antihypertensive treatment strategies.[2]	I	A
Combination treatment is recommended for most hypertensive patients as initial therapy. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or diuretic. Other combinations of the five major classes can be used.[233,318,327,329,341–345]	I	A
It is recommended that beta-blockers are combined with any of the other major drug classes when there are specific clinical situations, e.g. angina, post-myocardial infarction, heart failure, or heart rate control.[300,341]	I	A
It is recommended to initiate an antihypertensive treatment with a two-drug combination, preferably in an SPC. Exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is <150 mmHg).[342,346,351]	I	B
It is recommended that if BP is not controlled[c] with a two-drug combination, treatment should be increased to a three-drug combination, usually a RAS blocker with a CCB and a thiazide/thiazide-like diuretic, preferably as an SPC.[349,350]	I	A
It is recommended that if BP is not controlled[c] with a three-drug combination, treatment should be increased by the addition of spironolactone or, if not tolerated, other diuretics such as amiloride or higher doses of other diuretics, a beta-blocker, or an alpha-blocker.[310]	I	B
The combination of two RAS blockers is not recommended.[291,298,299]	III	A

Another example from the American Pain Society is equally salutary, stating that

> When considering initiation of methadone, … recommends that clinicians perform an individualized medical and behavioral risk evaluation to assess risks and benefits of methadone, given methadone's specific pharmacologic properties and adverse effect profile (strong recommendation, low-quality evidence).[3]

A strong recommendation, low-quality evidence is the least that will be accepted by any doctor as the basis for prescribing a drug. This article will not dwell on the importance of evidence-based medicine as the readers of this journal are fully cognizant of such matters. However, the MC industry is not traditional pharma and may not be aware of the ramifications and requirements for marketing a drug to doctors. The demonstration of non-inferiority of MC to extant treatment, or better still, superiority, is mandatory.

How can this be done? If a suitable product exists, creating the requisite research for a particular indication requires a plethora of disparate skills:

- Create a convincing proposal for a double-blind RCT.
  - Based on exhaustive literature review.
  - Including clear consent forms.
- Apply for ethical approval and data protection approval.
- Find a grant/funding.
- Register the study - internationally.
- Purchase insurance
- Enroll subjects: recruitment, informed consent.
- Run the study.
- Collect the data.
- Analyse it.
- Write a paper draft.
- Present at conferences:
  - A compelling abstract.
  - An attractive poster.
  - A captivating presentation.
- Professionally lay out a paper.
- Know which journals to target.
- Understand journal editors.
- Negotiate the peer-review process.
- Consider open-access publication.

Once several studies are in hand, a systematic review may be carried out e.g. using the PICO framework (**p**atient, **p**roblem or **p**opulation; **i**ntervention; **c**omparison, **c**ontrol or **c**omparator and **o**utcome).[4]

MC currently incorporate relatively few commercial products, and those that are developed and marketed with standardized ingredients and with the requisite quality control (e.g. nabilone) have been welcomed by the medical community as they permit proper RCTs. Thus far however, MC has not been shown to be terribly effective and has been associated with significant side effects.[5]

Clearly, new products and more clinical trials are required, since currently, patients preference for cannabinoids exceeds cannabinoids effectiveness.[6] These will take time and will cost money. For example, for a modelled, pharmaceutical industry-sponsored trial with 20 subjects required:

- Circa 4,012 man hours.
- 17 office visits/patient.
- Circa 200 hours/patient.
- 32% of total hours devoted to nonclinical activities related to
  - Institutional review board submission.
  - Completion of clinical reporting forms.

Thus, excluding overheads, this was estimated to cost circa $6,000 per enrolled subject, including $2,000 devoted to nonclinical costs, and this was back in 2003 with 20 subjects.[7] The reality is that studies are usually far larger. For example, the 2017 CANTOS trial of the anti-inflammatory drug canakinumab (Ilaris, Novartis) enrolled 10,000 cardiovascular high-risk patients.[8]

Current evidence

At the time of writing, evidence for the usefulness of MC is limited. For example, a recent (2017) review regarding MC effectiveness for the treatment of pain concluded that

> Evidence for inhaled marijuana for pain is too sparse and poor to provide good

> evidence-based guidance. Synthetic MC-derived products may modestly improve neuropathic pain for one in 11- 14 users but perhaps not for other pain types. Additionally, longer and larger studies (better evidence) show no effect. Adverse events are plentiful.[6]

Besides pain, a recent (2017) review with regard to the effectiveness for treatment of other conditions concluded that

> For most conditions (example anxiety), cannabinoid evidence is sparse (at best), low quality and non-convincing. Dronabinol/nabilone improve control of nausea/vomiting post chemotherapy for 1 in 3 users over placebo. Nabiximols likely improve multiple sclerosis spasticity ≥30% for ~1 in 10 users over placebo.[6]

With regard to epilepsy, a recent (2018) systematic review and meta-analysis on the efficacy and safety of cannabidiol concluded that

> AEs significantly associated with CBD were somnolence, decreased appetite, diarrhea, and increased serum aminotransferases…Adjunctive CBD in patients with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) experiencing seizures uncontrolled by concomitant anti- epileptic treatment regimens is associated with a greater reduction in seizure frequency and a higher rate of AEs than placebo.[9]

A recent (2018) review of the role of cannabis in the management of inflammatory bowel disease commissioned by the Crohn's and Colitis Foundation noted that

> Human studies have found benefit in controlling symptoms and improving quality of life, but no studies have established true disease modification given the absent improvement in biomarker profiles or endoscopic healing.[10]

Side effects

MC is also plagued by a significant risk of adverse effects, which are well known, and unexpected effects also frequently manifest. For example, cannabis use increases risk for revision after total knee arthroplasty.[11]

Another alarming example is that marijuana was found to have induced a Type I Brugada Pattern in a patient in whom this could not later be provoked with procamide challenge.[12] Indeed a recent (2017) review with regard to the harms associated with MC therapy concluded that

> Compared to placebo, medical cannabinoids cause multiple different adverse events in patients, from visual disturbance or hypotension (1 in 3-10) to hallucination or paranoia (1 in 20).
>
> Stopping due to adverse effects occurs in 1 in every 8-20 patients. Regardless of the type of medical cannabinoid used, adverse events are common and likely underestimated. Given the extensive harms, potential benefits must be impressive to warrant a trial of therapy.[13]

Additionally, concern has been raised by the finding that chronic marijuana use predominantly affects brain regions that supervise critical thought processes, such as attention, memory, and social interactions. The authors concluded that

> Disruption of these areas has been documented in schizophrenia and Alzheimer's disease, illnesses with symptoms and brain changes that parallel findings in marijuana abusers. These findings counter the claim that marijuana is a harmless drug and are a cause for alarm in persons with cannabis dependence.[14]

Conclusion

Extant data/product/s may not even be representative for the purposes for which MC is sought. There is clearly a knowledge gap must be bridged if MC is to ever be treated as medicine and routinely prescribed. MC must meet the same exacting standards of quality, effectiveness and safety of any other prescription drug or it risks being ignored or marginalized by the medical community. Indeed,

> The medical community assumes a contradictory stance toward medical

> marijuana (MM). Health care providers use the agent clinically…However, most professional medical associations do not offer clinical guidance on the subject, medical practice infrastructure does not always take MM into account, and some physicians who recommend MM clinically acknowledge that they do not understand it well enough to do so.[15]

MC is thus at a crossroads and must decide whether to continue as is, with equivocal studies and remain marginally used, largely a last ditch prescription mostly due to side effects. Or to improve and prove the value of extant and new products with RCTs that will lead to the inclusion of MC in medical society guidelines, ensuring their wider and useful use.

For all of these reasons, including the many unanswered questions, the MC industry constitutes an exciting and lucrative opportunity for Malta.

References

1. Appel JM. " Physicians are not Bootleggers": The Short, Peculiar Life of the Medicinal Alcohol Movement. Bull Hist Med. 2008 Summer;82(2):355-86
2. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement D, Coca A, De Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen S, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder R, Shlyakhto E, Tsioufis K, Aboyans V, Desormais I; List of authors/Task Force members. 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology: ESH/ESC Task Force for the Management of Arterial Hypertension. J Hypertens. 2018 Dec;36(12):2284-2309.
3. Chou R, Cruciani RA, Fiellin DA, Compton P, Farrar JT, Haigney MC, Inturrisi C, Knight JR, Otis-Green S, Marcus SM, Mehta D, Meyer MC, Portenoy R, Savage S, Strain E, Walsh S, Zeltzer L1 American Pain Society; Heart Rhythm Society. Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. J Pain. 2014 Apr;15(4):321-37.
4. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. BMC Med Inform Decis Mak. 2007 Jun 15;7:16.
5. MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. Eur J Intern Med. 2018 Mar;49:12-19.
6. Alberta College of Family Physicians. Any Other Doobieous Effects of Medical Cannabinoids? Tools for Practice. 2017; December. https://www.acfp.ca/wp-content/uploads/tools-for-practice/1512754221_tfp201medcanotherfv.pdf . Accessed 13/11/18
7. Emanuel EJ, Schnipper LE, Kamin DY, Levinson J, Lichter AS. The costs of conducting clinical research. J Clin Oncol. 2003 Nov 15;21(22):4145-50.
8. Ridker PM, Libby P, MacFadyen JG, Thuren T, Ballantyne C, Fonseca F, Koenig W, Shimokawa H, Everett BM, Glynn RJ. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). Eur Heart J. 2018 Oct 7;39(38):3499-3507.
9. Lattanzi S, Brigo F, Trinka E, Zaccara G, Cagnetti C, Del Giovane C, Silvestrini M. Efficacy and Safety of Cannabidiol in Epilepsy: A Systematic Review and Meta-Analysis. Drugs. 2018 Nov 3. doi: 10.1007/s40265-018-0992-5.
10. Swaminath A, Berlin EP, Cheifetz A, Hoffenberg E, Kinnucan J, Wingate L, Buchanan S, Zmeter N, Rubin DT. The Role of Cannabis in the Management of Inflammatory Bowel Disease: A Review of Clinical, Scientific, and Regulatory Information: Commissioned by the Crohn's and Colitis Foundation. Inflamm Bowel Dis. 2018 Oct 24. doi: 10.1093/ibd/izy319.
11. Law TY, Kurowicki J, Rosas S, Sabeh K, Summers S, Hubbard Z, Roche M. Cannabis use increases risk for revision after total knee arthroplasty. J Long Term Eff Med Implants. 2018;28(2):125-130. doi: 10.1615/JLongTermEffMedImplants.2018027401.
12. Kariyanna PT, Jayarangaiah A, Hegde S, Marmur JD, Wengrofsky P, Yacoub M, Post M, McFarlane SI. Marijuana Induced Type I Brugada Pattern: A Case Report. Am J Med Case Rep. 2018;6(7):134-136.
13. Alberta College of Family Physicians. Harms of Medical Cannabinoids: Up in Smoke! Tools for Practice. 2017; December. https://www.acfp.ca/wp-content/uploads/tools-for-practice/1511480622_tfp200harmsmmfv.pdf. Accessed 13/11/18.
14. Stoecker WV, Rapp EE, Malters JM. Marijuana Use in the Era of Changing Cannabis Laws: What Are the Risks? Who is Most at Risk? Mo Med. 2018 Sep-Oct;115(5):398-404.
15. Braun I, Tulsky J. Reconciling the Discrepancies in Medicine's Relationship to Medical Marijuana. Ann Intern Med. 2018;169(9):646-7.

Cover Picture:
'Valletta'
Maltese lace (Bizzilla)
By Sr Therese Bajada

Review Article

Measles is back

Ruth Farrugia, David Pace

Abstract

Measles is one of the most deadly vaccine preventable diseases. The incidence of measles, and resultant mortality, had dropped drastically following the introduction of widespread measles immunisation since the 1960s. However, there is currently a worldwide surge in measles cases, with a marked increase over the past 3 years. Measles outbreaks and endemic transmission have been re-established in countries which had previously achieved measles elimination. The rise in measles cases has been mainly attributed to a drop in the recommended two dose vaccination schedule below the 95% uptake threshold necessary for interruption of transmission and sustainment of herd protection. This resurgence of measles is largely a result of the damage done by Andrew Wakefield, who in 1998 incorrectly and maliciously suggested a possible link between the measles, mumps and rubella (MMR) vaccine and autism. Such a possible association has subsequently been disproven by several scientifically robust studies. Still, most cases of measles have occurred in unimmunised individuals, mainly teenagers, who had missed out on vaccination in early childhood, and in infants under one year of age, who are too young to be vaccinated. Measles is highly contagious, with up to 18 people being potentially infected from a single case, so containment measures are important to prevent spread. These include isolation and immediate notification of suspected or confirmed cases, as well as wearing appropriate personal protective equipment when in contact with these patients. Health care professionals have a crucial role in promoting measles immunisation, which is the only rational way of preventing measles.

Ruth Farrugia*, MD, MRCPCH (UK), MSc PEM (Edin)
ruth.b.farrugia@gov.mt

David Pace, MD, Pg Dip PID (Oxf), FRCPCH, PhD

**Corresponding author*

Measles is one of the most deadly vaccine-preventable diseases[1] and is included in the top overall causes of death in children under 5 years of age worldwide.[2]

Prior to the introduction of widespread measles vaccination in 1963, measles accounted for about 2.6 million deaths annually.[3] In fact, one of the aims of the Global Vaccine Action Plan 2011 – 2020[4] was the elimination of measles in 4 out of 5 World Health Organization (WHO) regions by 2015, but this aim has not been achieved.[5] Measles elimination is defined as the absence of endemic measles virus transmission in a region or other defined geographic area for ≥12 months, in the presence of a high quality surveillance system that meets targets of key performance indicators.[6]

In theory, eradication of measles is possible because humans are the only reservoirs,[7] measles is only infectious during the acute phase,[7] specific and rapid diagnostic tests are available,[8] the measles virus is monotypic[8] and a monovalent vaccine is effective against all known virus isolates.[8]

The measles virus is aerosol-borne and is easily spread by coughing and sneezing, close personal contact or direct contact with infected nasal or throat secretions.[3] Measles is highly contagious, starting from four days prior onset of the rash until four days following rash appearance.[1] Over 90% of contacts develop the disease.[9] The basic reproduction number (R_0) for measles lies between 12 and 18,[10] meaning that a single patient with measles may infect up to 18 susceptible people.[9] In comparison, R_0 for influenza is estimated between 2 and 4[11] while R_0 for varicella ranges between 3.7 and 5.[12]

The clinical description for measles by the Centers for Disease Control and Prevention (CDC) states that measles is an acute illness characterised by a generalised maculopapular rash that is present for at least 3 days, an oral temperature of at least 101℉ (38.3℃) and the presence of cough, coryza, and conjunctivitis.[13] The pathognomonic Koplik spots on the buccal mucosa, which are not always present, are not a diagnostic criterion.[7] The incubation period for measles is 10 days for onset

of fever; the rash usually appears 4 days later.[7] Laboratory diagnosis, which is a requisite for case confirmation, may be performed by detecting measles IgM in serum or saliva.[14] Of note, 30% may be negative in the initial 3 days and the tests should not be performed later than 4 weeks from onset of the rash.[15] False positives may occur especially with rubella and parvovirus B19 infections.[16] PCR testing on respiratory secretions, nasopharyngeal swab, blood or urine may be needed for genetic characterisation of the virus, which can help identify the source of infection.[17] There is no specific treatment for measles.

Measles complications can occur in up to 40% of patients and are more common in high-risk patients.[7] Pneumonia occurs in up to 1 in 16 patients[18] and is the leading cause of measles-associated death.[1] Other complications include otitis media (in about 1 in 12 measles cases)[18], diarrhoea (in about 1 in 12 measles cases),[18] ocular complications and central nervous system manifestations, such as encephalitis (in about 1 in every 1000 - 2000 measles cases)[18] or subacute sclerosing panencephalitis (in about 4 - 11 per 100,000 measles cases).[1] Measles also causes long-lasting memory B and T cell impairment.[19] High-risk patients include immunosuppressed patients (in whom typical signs and symptoms may be absent), patients with Vitamin A deficiency, malnourished patients and travellers.[7] Young infants also have a higher risk of mortality and complications,[7] especially if born to mothers with vaccine-derived immunity or who are infected with HIV.[20] Passive immunity lasts longer in mothers with natural immunity to measles but by 6 months of age less than 5% of all infants retain maternal antibodies.[21]

A proportion of individuals with measles will need hospital admission. Unfortunately, hospital admission is associated with measles transmission,[22] including outbreaks amongst healthcare workers.[23] The cost of delay in diagnosis and the resultant potential exposure is prohibitive, in view of the high infectivity of measles.[24] Patients suspected of having measles should be isolated immediately and measures should be in place to prevent further spread during outbreaks. The virus remains infective for two hours on solid surfaces, which should be borne in mind when decontaminating a room.[25] Infection control measures should be implemented as per local recommendations and respiratory protection by means of N95 or FFP3 (filtering facepiece class 3) mask should be worn when attending to a patient with suspected or confirmed measles,[26] irrespective of the immunity of the healthcare worker to measles. A normal surgical mask should be worn if a FFP is not available – this will still provide a reasonable level of protection.[27]

The only rational way of preventing measles in a population is through vaccination. The MMR (measles, mumps, rubella) vaccine has 99% effectiveness against measles following 2 doses,[28] is well tolerated, safe,[29] and offers long-lasting protection.[30] In fact, measles vaccination is estimated to have prevented 20.4 million deaths between 2000 – 2016.[31] However, in view of the high R_0 for measles, a high uptake of at least 95% for both doses is needed in order to eliminate measles from a population and to attain herd protection.[32-33]

In Malta, the first dose of MMR vaccine is administered at 13 months of age, with the second dose being given at 3 to 4 years of age.[34] This is in line with the WHO recommendations that two doses of measles-containing vaccine, such as the MMR vaccine, for countries with low risk of measles should be given at around 12 months of age for the first dose and that the second dose of MMR vaccine should be given at the age when maximum coverage at national level is anticipated.[35] A supplementary dose of measles vaccine is recommended from 6 months of age onwards during measles outbreaks[35]. Any dose of measles vaccine given before 12 months of age should not be counted as part of the series and these children should be revaccinated with 2 doses of the MMR vaccine after 12 months of age.[36]

Unfortunately, measles immunisation rates have dropped globally. During 2017, 85% of children received one dose of measles vaccine by their second birthday, with only 67% receiving the second dose as part of routine immunisation.[37] In Europe, immunisation rates for 2017 were 95% for the first dose and 90% for the second dose.[38] The single most influential factor for the drop in measles vaccine uptake was an article by Dr Andrew Wakefield in The Lancet in 1998,[39] which suggested a potential link between the MMR vaccine and developmental regression and autism, among other conditions. This paper received disproportionate media coverage and caused the biggest public health scare in UK history.[40] Flaws

in research methods were immediately pointed out, including that it was a case series of 12 children without controls and that data collection relied on parent's personal beliefs and recalls.[41] Large epidemiological studies over the years,[42-46] as well as a WHO extensive review[47] and a Cochrane systematic review,[48] have since disproved any links between the MMR vaccine and autism. The UK General Medical Council found that Dr Wakefield had falsified his data and had breached ethical standards in this publication[49] and consequently he was struck off the register because of his serious professional misconduct.[50] The paper was also withdrawn by The Lancet in 2010.[51] However, it is still widely quoted by anti-vaccine campaigners and parents, some of whom remain unsure whom to believe, despite all the robust scientific evidence proving that the MMR vaccine is not associated with autism.[52]

Endemic transmission of measles can be re-established once vaccination rates fall below the elimination threshold.[53] In fact, measles has again become endemic in all five WHO regions during 2018, with the rate of measles being the highest in a decade[54] and continuing to rise by a further 300% during the first quarter of 2019.[55] Over 82,000 people in the WHO European region contracted measles during 2018, with up to 61% needing hospitalisation and 72 deaths in children and adults.[38] This is more than three times as many as in 2017, 15 times as many as in 2016[18] and even surpassed the number of measles cases in the WHO African region in 2018, which totalled 33,879.[56] This figure includes national outbreaks in countries having previously achieved measles elimination, such as The Netherlands[57] and Greece,[58] and also the re-establishment of endemic transmission in countries where measles had been eliminated, as happened in the United Kingdom.[59]

Malta has maintained the status of measles elimination in 2018, because there have not been any cases of measles due to sustained transmission.[60] However, there is an increasing trend in locally acquired measles, rising from 6 cases in 2018[60] to 15 confirmed cases so by April 2019 - 23 cases in adults and 2 cases in children.[61] During 2018, 95.5% of children in Malta received the first dose of MMR and 95% received the second dose of MMR vaccine.[62] This is in contrast to previous years, when immunisation rates in Malta had dropped below the 95% uptake rate (for both doses) needed to prevent disease transmission. In fact, only 91% of children received the first dose of MMR vaccine and 83% received the second dose during 2017[63], although this could be a result of inadequate notification. This is the ideal scenario for breakthrough cases of measles and, in the absence of herd protection, the potential for outbreaks, as has happened in other countries.

Indeed, the surge in measles in Europe has been mainly attributed to a drop in two-dose measles vaccine coverage below 95% and a drop in prevalence of individuals with vaccine-induced protection of measles to less than 94.4%.[64] Out of the 14,400 reported cases of measles in Europe in 2017[65] with known vaccination status, 87% were unimmunised, 8% had received one dose of measles-containing vaccine, 3% had received two or more doses of vaccine and 2% were vaccinated with an unknown number of doses.[66] Immunisation status was unknown for 6%.[66] Thirty seven percent of measles occurred in children under 5 years of age, with the highest disease burden occurring in children below the age of 1 year, while 45% occurred in patients older that fifteen years.[66] Therefore, nearly half of the measles cases in Europe occurred in unimmunised adolescents aged 15 years or older, highlighting the need to identify and catch-up those who missed out on routine vaccination in childhood.

The resurgence of measles at a global level is being driven by multiple factors, including conflict, poor health education, lack of access to health care, complacency, increasing vaccine hesitancy and low support amongst medical personnel.[67] In addition, vaccine coverage may be suboptimal in at-risk groups, including Roma, Irish travellers, orthodox religious communities[67] and adolescent and adult migrants, who might be excluded from the immunisation catch-up initiatives provided to younger children.[68] Failure to address vaccination shortfalls in vulnerable populations will create immunisation gaps and lead to subnational coverage.

Measles is a vaccine-preventable disease which carries a high morbidity and mortality. Elimination of measles is dependent on sustaining herd protection and in limiting transmission during outbreaks. Our role as health care professionals is to actively encourage MMR vaccine uptake, including opportunistic vaccination for those who were not immunised at the appropriate times, address public

concerns, expedite the diagnosis of measles, notify immediately any suspected or confirmed cases and help in containing outbreaks.

References

1. Buchanan R, Bonthius D. Measles virus and associated central nervous system sequelae. Seminars in paediatric neurology. 2012;19(3):107-4.
2. World Health Organization. Global Health Observatory data: Causes of Child Mortality, 2017. [Internet]. 2018 [cited 8th April 2019]. Available from: https://www.who.int/gho/child_health/mortality/causes/en/
3. World Health Organization. Measles Fact Sheet. [Internet]. 2018 [cited 28th March 2019];Nov 29. Available from: https://www.who.int/news-room/fact-sheets/detail/measles
4. World Health Organization. Global Vaccine Action Plan 2011 – 2020. [Internet]. 2013 [cited 8th April 2019]. Available from: https://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/
5. World Health Organization Resolution. Renewed commitment to elimination of measles and rubella and prevention of congenital rubella syndrome by 2015 and sustained support for polio-free status in the WHO European region. WHO Regional Office for Europe, Moscow, Russia. [Internet]. 2010 [cited 8th April 2019]. Available from: http://www. euro.who.int/__data/assets/pdf_file/0016/122236/RC60_eRes12. pdf
6. World Health Organization. Monitoring progress towards measles elimination. Weekly epidemiological record. 2010;85:489-96.
7. Moss WJ, Griffin DE. Measles. Lancet. 2012;379:153-164.
8. Meissner HC, Sterbel PM, Orenstien WA. Measles vaccines and the potential for worldwide eradication of measles. Pediatrics. 2004;114:1065-1069.
9. Holzmann H, Hengel H et al. Eradication of measles: remaining challenges. Medical Microbiology and Immunology. 2016;March 2:1-8.
10. Guerra FM, Bolotin S et al. The basic reproduction number (R0) of measles: a systematic review. Lancet Infectious Diseases. 2017;17(12), e420–e428.
11. Scarbrough Lefebre CD, Terlinden A, Standaert B. Dissecting the indirect effects caused by vaccines into the basic elements. Human Vaccines and Immuotherapeutics. 2015;11(9):2142-2157.
12. Marangi L, Mirinaviciute G et al. The natural history of varicella zoster virus infection in Norway: Further insights on exogenous boosting and progressive immunity to herpes zoster. PLoS ONE 2017;12(5):e0176845.
13. Centers for Disease Control and Prevention. National Notifiable Diseases Surveillance System (NNDAA): Measles/Rubeola 2013 Case Definition [Internet]. 2013 [cited 8th April 2019]. Available from: https://wwwn.cdc.gov/nndss/conditions/measles/case-definition/2013/
14. Bellini WJ, Hefland RF. The challenges and strategies for laboratory diagnosis of measles in an international setting. Journal of Infectious Diseases. 2003;187(Suppl 1):S283-90.
15. Hefland RF, Kebede S et al. The effect of timing of sample collection on the detection of measles-specific IgM in serum and oral fluid samples after primary measles vaccination. Epidemiology and Infection. 1999;12(3):451-5.
16. Brown DWG, Ramsay MB et al. Salivary diagnosis of measles: A study of notified cases in the United Kingdom, 1991-1993. British Medical Journal. 1994;308(6395):1015-7.
17. Rota PA, Liffick SL et al. Molecular epidemiology of measles viruses in the United States, 1997-2001. Emerging Infectious Diseases. [Internet]. 2002 [cited 8th May 2016];8(9):902-908. Available online: http://wwwnc.cdc.gov/eid/article/8/9/02-0206_article
18. Oxford Vaccine Group. Vaccine Knowledge Project: Measles. [Internet]. 2019 [cited 1st April 2019]; Mar 7. Available from: http://vk.ovg.ox.ac.uk/measles
19. Mina MJ, Metcalf CJE et al. Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality. Science. 2015;348(6235):694-9.
20. Perry RT, Mmiro F et al. Measles infection in HIV-infected African infants. Annals of the New York Academy of Sciences. 2000;918:377-380.
21. Leuridan E, Hens N et al. Early waning of maternal measles antibodies in era of measles elimination: longitudinal study. British Medical Journal. 2010;340:c1626.
22. Hungerford D, Cleary P et al. Risk factors for transmission of measles during an outbreak: matched case-control study. Journal of Hospital Infection. 2014;86:138-43.
23. Duarte S. Practice what you preach: measles vaccination coverage and outbreaks in healthcare workers in Europe. European Journal of Public Health. 2018(28:4):381-382.
24. Helmecke MR, Elmendorf SL et al. Measles investigation: a moving target. American Journal of Infection Control. 2014;42:911-5.
25. Ritcher S, Hawkins A, Painter L. Measles on the rise: academic institutions be prepared. Perspectives in Learning: A Journal of the College of Education & Health Professions. [Internet]. 2012 [cited 1st April 2019];13(1):33-38. Available online: https://perspectives.columbusstate.edu/v13_i_1/MeaslesOnTheRise.pdf
26. European Centre for Disease Prevention and Control. Safe use of personal protective equipment in the treatment of infectious diseases of high consequence – version 2 [Internet]. 2014 [cited 8th April 2019];Dec 2. Available from: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/safe-use-of-ppe.pdf

27. Office of the Superintendent of Public Health. Letter to doctors [Internet]. 2018 [cited 8th April 2019]; Aug 1. Available from: https://deputyprimeminister.gov.mt/en/administration-and-communication/Documents/Circulars/Measles_Doctors_03.08.01.pdf
28. Pillsbury A, Quinn H. An assessment of measles vaccine effectiveness, Australia, 2006-2012. Western Pacific Surveillance and Response. 2015;6(3);43-50.
29. Klein NP, Lewis E et al. Safety of measles-containing vaccines in 1-year-old children. Pediatrics. 2015;135(2):2321-329.
30. Amanna IJ, Carlson NE, Slifka MK. Duration of humoral immunity to common viral and vaccine antigens. The New England Journal of Medicine. 2007;357:1903-1915.
31. Dabbagh A, Patel MK et al. Progress towards regional measles elimination - worldwide 2010 – 2016. Morbidity and Mortality Weekly Report; US Department of Health and Human Services/Centers for Disease Control and Prevention. 2017;66(42):1148-1153.
32. van Boven M, Kretzschmar M et al. Estimation of measles vaccine efficacy and critical vaccination coverage in a highly vaccinated population. Journal of the Royal Society Interface. 2010;7(52):1537-1544.
33. Glick M. Vaccine hesitancy and unfalsifiability. Journal of the American Dental Association. 2015;146(7):491-493.
34. Primary Health Care. National Immunisation Schedule 2017 [Internet]. 2017 [cited 8th April 2019]. Available from: https://deputyprimeminister.gov.mt/en/phc/pchyhi/Pages/National-Immunisation-Schedule.aspx
35. World Health Organization. Summary of the WHO position on measles vaccine – April 2017 [Internet]. 2017 [cited 8th April 2019]. Available from: https://www.who.int/immunization/policy/position_papers/WHO_PP_measles_vaccine_summary_2017.pdf?ua=1
36. Centers for Disease Control and Prevention. Epidemiology and prevention of vaccine-preventable diseases: measles [Internet]. Updated 2015 [cited 8th April 2019]; July 24. Available grom: https://www.cdc.gov/vaccines/pubs/pinkbook/meas.html
37. World Health Organization. Immunization Coverage [Internet]. 2018 [cited 8th April 2019]; July 16. Available from: https://www.who.int/en/news-room/fact-sheets/detail/immunization-coverage
38. World Health Organization. Measles in Europe: record number of both sick and immunized. [Internet]. 2019 [cited 28th March 2019]; Feb 7. Available from: http://www.euro.who.int/en/media-centre/sections/press-releases/2019/measles-in-europe-record-number-of-both-sick-and-immunized
39. Wakefield AJ, Murch SH et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. The Lancet. 1998;351:637-41.
40. Kmietowicz Z. Wakefield is struck off for the 'serious and wide-ranging findings against him'. British Medical Journal. 2010;340:c2803.
41. Payne C, Mason B. Autism, inflammatory bowel disease, and MMR vaccine. Lancet. 1998;351:907.
42. Black C, Kaye JA, Jick H. Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research Database. British Medical Journal. 2002;325:419-21.
43. Madsen KM, Hviid A et al. A population-based study of measles, mumps and rubella vaccination and autism. New England Journal of Medicine. 2002;347(19):1477-1482.
44. Taylor B, Miller E et al. Measles, mumps, and rubella vaccination and bowel problems or developmental regression in children with autism: population study. British Medical Journal. 2002;324(7334):393–396.
45. Honda H, Shimizu Y, Rutter M. No effect of MMR withdrawal on the incidence of autism: a total population study. Journal of Child Psychology and Psychiatry. 2005;46(6):572-579.
46. Hornig M, Briese T et al. Lack of Association between Measles Virus Vaccine and Autism with Enteropathy: A Case-Control Study. PLoS ONE 3(9): e3140.
47. World Health Organization. MMR and Autism. Weekly epidemiological record. 2003;78:18.
48. Demicheli V, Rivetti A et al. Vaccines for measles, mumps and rubella in children. Cochrane Database of Systematic Reviews. 2012, Issue 2, Art. No: CD004407.
49. "General Medical Council, Fitness to Practise Panel Hearing, 28 January 2010, Andrew Wakefield, John Walker Smith, Simon Murch". [Internet]. General Medical Council. 2010 [cited 8th April 2019], January 28. Available from: https://briandeer.com/solved/gmc-charge-sheet.pdf
50. "General Medical Council, Fitness to Practise Panel Hearing, 24 May 2010, Andrew Wakefield, Determination of Serious Professional Misconduct". [Internet]. General Medical Council. 2010 [cited 8th April 2019], May 24. Available from: https://web.archive.org/web/20110809092833/http://www.gmc-uk.org/Wakefield_SPM_and_SANCTION.pdf_32595267.pdf
51. The editors of the Lancet. Retraction - Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet. 2010;375:445.
52. Hilton S, Petticrew M, Hunt K. Parents' champions vs. vested interests: Who do parents believe about MMR? A qualitative study. BMC Public Health. 2007;7:42.
53. Bester JC. Measles and measles vaccination – a review. JAMA Pediatrics. 2016(Oct 3):E1-E7.
54. World Health Organization. 2018 Assessment report of the global vaccine action plan. [Internet]. 2018 [cited 1st April 2019]. Available from: https://www.who.int/immunization/global_vaccine_action_plan/SAGE_GVAP_Assessment_Report_2018_EN.pdf?ua=1
55. World Health Organization. New measles surveillance data for 2019. [Internet]. 2019 [cited 15th April 2019]; Apr 15. Available from: https://www.who.int/immunization/newsroom/measles-data-2019/en/

56. United Nations. Measles cases nearly doubled in a year, UN health agency projects. [Internet]. 2019 [cited 28th March 2019]; Feb 14. Available from: https://news.un.org/en/story/2019/02/1032771
57. Knol M, Urbanus A et al. Large ongoing measles outbreak in a religious community in the Netherlands since May 2013. Euro Surveillance. 2013;18(36):20580.
58. Georgakopoulou T, Horefti E et al. Ongoing measles outbreak in Greece related to the recent European-wide epidemic. Epidemiology and Infection.2018;147(13):1692-8.
59. Measles once again endemic in the United Kingdom. Euro Surveillance. 2008;13(27):18919.
60. Superintenence of Public Health. Press release PR190563 [Internet]. 2019 [cited 28th march 2019]; Mar 19. Available from: https://www.gov.mt/en/Government/DOI/Press%20Releases/Pages/2019/March/19/pr190563.aspx
61. Office of the Superintendent of Public Health, Malta. Information sheet measles [email]. 2019; April 26.
62. Data obtained from National Immunisation Programme, Floriana. Personal communication with Dr Victoria Farrugia Sant'Angelo. 2019; April 29.
63. World Health Organization. WHO vaccine-preventable diseases: monitoring system. 2018 global summary. [Internet]. 2018 [cited 8th April 2019];Oct 22. Available from: https://apps.who.int/immunization_monitoring/globalsummary/countries?countrycriteria%5Bcountry%5D%5B%5D=MLT#
64. Plans-Rubio P. Why does measles persist in Europe? European Journal of Clinical Microbiology and Infectious Diseases. 2017;Oct;36(10):1899-1906.
65. European Centre for Disease Prevention and Control. Measles and rubella surveillance – 2017. [Internet]. 2018 [cited 28th March 2019]; Apr 23. Available from: https://ecdc.europa.eu/en/publications-data/annual-measles-and-rubella-monitoring-report-2017
66. European Centre for Disease Prevention and Control. Risk of measles transmission in the EU/EAA. [Internet]. 2018 [cited 28th March 2019]; March 23. Available from: https://ecdc.europa.eu/sites/portal/files/documents/Measles-rapid-risk-assessment-European-Union-countries_0.pdf
67. Williams GA, Bacci S et al. Measles among migrants in the European Union and the European Economic Area. Scandinavian Journal of Public Health. 2016;44:6-13.
68. Hargreaves S, Nellums LB et al. Who is responsible for the vaccination of migrants in Europe? Lancet. 2018;391(10132):1752-4.

Review Article

Climate change and human illness: a hot topic?

Paul Torpiano

Abstract

Global climate change, now proven to occur under the influence of human activity, affects human health and illness. Aside from the risk of natural disasters and diminishing fresh-water supply and arable land, climate change maintains a complex relationship with both communicable and non-communicable forms of illness. The epidemiology of infectious diseases, whether viral, parasitic, or bacterial, has shown to change under the influence of climate, particularly in the case of vector-borne zoonoses. Non-communicable disease, , including allergic, respiratory, cardiovascular and dermatological, are also influenced by global and regional changes in climate. While undoubtedly of increasing importance, the role of the clinician in educating communities on the negative health impact of climate change, as well as the potential benefit of sustainable healthcare policy, are yet to be defined.

Paul Torpiano MD, MRCPCH (UK), MRCP (UK), PGDip PID (Oxford)
Department of Paediatrics
Mater Dei Hospital
Msida, Malta
paul.torpiano@gov.mt

Background

That climate change is real, and that it is anthropogenic, is now beyond doubt. Evidence to this effect is now in abundance: rising seas levels, otherwise inexplicable patterns of global warming over the last 50 years, reductions in arctic sea ice, an increase in the frequency of intense tropical cyclones.[1] Scientists now forecast that global temperatures may rise between 1.4-5.8ºC by the year 2100.[2] Global climate change is caused by several interacting mechanisms: human production of greenhouse gases, stratospheric ozone depletion, and increasing volcanic activity.[2] Since the mid-19th century, human activities have generated increasing amounts of greenhouse gases, including carbon dioxide, methane, and nitrous oxide, resulting in increased average temperature.[3] The effects of this include soil degradation and loss of agricultural land, desertification, loss of biodiversity, and declining fresh-water resources.[3] The global conversation has now shifted, with the focus now on the impact of climate change on human health, and what can be done to mitigate this.

Many of the negative effects of climate change are self-evident. Changing patterns of rainfall, leading to drought and mass dehydration in some areas, while fierce tropical cyclones batter others, puts lives at risk.[4] The same can be said of tsunami, tectonic and volcanic activity, floods, and other natural disasters, the frequency of which are influenced by widespread climate change.[4] Aside from deaths from drowning or trauma, natural disasters can damage global food supplies, leading to famine, and lead to large-scale migration of at-risk populations.[4] But beyond natural disasters, how does climate change influence the epidemiology and outcome of human illness?

Predictions from the past

Warnings of the potential for climate change to impact human health are not new. In a 1991 paper entitled ‘Anticipated public health

consequences of global climate change', Janice Longstreth suggested that rising temperatures could cause decompensation in those with chronic cardiovascular or respiratory disease. She flagged up the potential for climate change to cause an increase in asthmatic exacerbations, lung malignancy, and vector-borne illnesses, while suggesting that the impact on forests and wetlands could influence the airborne concentration of allergens such as moulds and pollens.[5] This, in turn, could alter the epidemiology of eczema, asthma, allergic rhinitis, and other atopy-related illness.[5] Rising sea levels secondary to melting polar ice caps could restrict habitable terrain, leading to overcrowded residential areas.[5] Urbach et al indicated that increases in ultraviolet radiation could cause surges in skin malignancy, cataracts, and even alter the immune system.[6] Other reports highlighted the potential for climate change to affect fertility rates, neonatal development, perinatal mortality, and preterm birth rates.[5,7-8] Kalkstein et al used mathematical modelling based on global warming to warn of significant increases in weather-related mortality,[9] while McGeehin et al proposed that mortality and morbidity secondary to climate change would depend on the readiness of a population to adapt physiologically and behaviourally to temperature changes. In this model, the elderly, young children, and those of low socio-economic status were shown to be particularly vulnerable.[10]

Communicable disease

Changes in temperature and rainfall patterns, particularly extreme weather events, enhance the spread of infectious diseases.[11] The life cycles and epidemiology of infectious organisms are intimately related to the environment, and as such, are subject to the influence of climate. There is convincing evidence that diarrhoeal diseases increase with rising temperatures, with an estimated increased risk of 3-11% for every 1ºC of environmental temperature rise.[12] *Salmonella sp.* and *Vibrio cholerae*, both important causes of diarrhoeal disease in low and middle income countries, proliferate more rapidly at higher temperatures.[13] Changing rainfall patterns may cause floods, with subsequent epidemics of leptospirosis, campylobacteriosis and cryptosporidiosis.[3] While increasing global temperatures could be expected to lead to a fall in Winter respiratory infections, the relationships between the climate and the causative pathogens appear to be complex. In fact, fluctuating temperatures may increase the incidence and mortality of viral respiratory infections amongst vulnerable populations, such as older adults and children.[14]

Pathogens transmitted by vectors are particularly sensitive to climate change, since they are often carried by cold-blooded intervertebrate hosts whose temperature reflects that of the environment.[3] Warmer climates can present more favourable conditions for the completion of a life cycle, as in the case of mosquitos.[3] In addition, climate change will undoubtedly cause behavioural changes amongst the hosts of such pathogens. Such changes could influence migration, feeding, and reproductive behaviour, with the potential to affect human contact with these hosts.[3] A recent report highlighted the importance of climate change and exposure to prairie dogs, a common reservoir for *Yersinia pestis*, as the source of a pulmonary plague outbreak in Colorado.[15] Statistical models defining the relationship between climate change and vectors of other bacterial diseases, such as leptospirosis, have also predicted predict future epidemics.[16] Tick-borne illnesses, such as Mediterranean Spotted Fever, have shown increases in cold regions in recent years, possibly as a result of rising temperatures that encourage egg production and biting behavior amongst ticks.[17] Lyme disease, another tick-borne illness caused by *Borrelia burgdorferi*, has seen its area of endemicity and incidence increase in the United States.[18] Dry weather has also resulted in significantly increased rates, geographic range, and infectious cycles of leishmaniasis in the US, potentially due to northward extension of the rodent reservoir and sand fly vectors, *Lutzomyia diabolica* and *Lutzomyia anthrophora*.[19] Furthermore, climate change has been linked to increases in a number of infectious skin pathologies, including cercarial dermatitis, cellulitis and wound infections with *Vibrio parahaemolyticus* and *Vibrio vulnificus*, and melioidosis.[20]

Malaria, still the most common cause of arthropod-borne infectious disease worldwide, has become endemic at higher altitudes and in new, formerly malaria-free tropical, subtropical and temperate regions. This has most probably occurred under the influence of global warming and increasing precipitation in these areas.[2] The link

between malaria and weather patterns has been visible elsewhere: studies in South Asia and South America documented an association between malaria outbreaks and the El Nino Southern Oscillation cycle.[21–23] Such an association has also explained similar outbreaks of dengue fever in these regions.[24] The West Nile virus, which utilizes birds as a reservoir and mosquitoes as vectors, has gained prominence in the Mediterranean area and North America over recent years.[25] The incidence of another viral infection, enteroviral hand-foot-and-mouth disease (HFM), shows correlation with average temperature and rainfall, while humidity has been associated with HFM epidemics.[26]

Non-communicable disease

The influence of climate on non-communicable disease may be less apparent. As alluded to earlier, a changing climate will alter distribution of vegetation and forestation, with a likely impact on pollens and other airborne allergens. Higher levels of carbon dioxide, together with a warmer climate, could cause anticipation in time of the onset of warmer seasons and thus of the concentration of aeroallergens.[12] Studies in the Eastern Mediterranean region have shown that an earlier and longer-lasting presence of aeroallergens exacerbates allergic rhinitis, asthma, and eczema.[27-28] Increases in ambient pollen concentrations are associated with higher rates of allergic sensitization, higher numbers of emergency department visits and hospital admissions for asthma and allergic rhinitis, as well as higher numbers of physician office visits for allergic diseases.[29]

Beyond allergy, the cardiorespiratory system may be vulnerable to climate change by additional mechanisms. A review published in 2007 by the US Environmental Protection Agency concluded that high ozone exposure owing to heat waves was associated with a reduction in lung function and exacerbation of respiratory symptoms in patients with pre-existing respiratory diseases, contributing to premature deaths in people with heart and lung disease.[30] Warmer temperatures appear to increase the concentrations of air pollutants, mainly ozone and particulate matter that are of particular relevance for cardiopulmonary health.[31] A case-crossover study in England and Wales examining the relationship between temperature and the incidence of acute myocardial infarction found that increasing ambient temperatures above a threshold of 20 °C were associated with a higher risk of myocardial infarction occurring as early as 1 to 6 h after exposure.[32] This link between myocardial infarction and higher temperatures has since been described further in a recent systematic review.[33]

Changes in ambient temperature and sun exposure would be expected to influence skin disease. Ozone depletion has resulted in an increased risk of skin cancer, while elevated temperatures alone could result in increased ultraviolet damage to skin, even without changes in ultraviolet light dose.[34-35] A 2ºC temperature rise may increase the number of skin cancers yearly by 10%.[36] Warmer temperatures are also associated with increased time spent outdoors, often without protective clothing or sunblock.[37] Furthermore, warmer oceans generate larger jellyfish populations, with a recent systematic review confirming a worldwide increase.[38] This puts swimmers at increased risk of jellyfish-related stings.

Conclusions

As our understanding of the mechanisms and impact of climate change improves, the knowledge-base surrounding the influence of climate change on human illness will also expand. Research carried out in the last decade has proven correct many of the predictions made earlier concerning how climate change might affect our health, while revealing some surprises about the complex relationship between climate and disease. Both communicable and non-communicable illnesses have been shown to act under the influence of climate. Further research, along with close epidemiological surveillance of disease, will help shed more light on this relevant area of study, and may guide both health and enivironmental policy in the years to come. As the link between climate and disease becomes clearer, so will our responsibility as clinicians to educate patients and communities on the health-related dangers of unsustainable behaviours and global environmental change.[39]

References

1. 9.7 Combining Evidence of Anthropogenic Climate Change - AR4 WGI Chapter 9: Understanding and Attributing Climate Change. https://www.ipcc.ch/publications_and_data/ar4/wg1/en/ch9s9-7.html#table-9-4. Accessed January 31, 2018.
2. Diaz JH. Global Climate Changes, Natural Disasters, and Travel Health Risks. *J Travel Med.* 2006;13(6):361-372. doi:10.1111/j.1708-8305.2006.00072.x.

3. Rossati A. Global Warming and Its Health Impact. *Int J Occup Environ Med*. 2017;8(1):7-20. doi:10.15171/ijoem.2017.963.
4. Diaz JH. The influence of global warming on natural disasters and their public health outcomes. *Am J Disaster Med*. 2(1):33-42. http://www.ncbi.nlm.nih.gov/pubmed/18268873. Accessed September 23, 2017.
5. Longstreth J. Anticipated public health consequences of global climate change. *Environ Health Perspect*. 1991;96:139-144. http://www.ncbi.nlm.nih.gov/pubmed/1820256. Accessed September 24, 2017.
6. Urbach F. Potential health effects of climatic change: effects of increased ultraviolet radiation on man. *Environ Health Perspect*. 1991;96:175-176. http://www.ncbi.nlm.nih.gov/pubmed/1820263. Accessed January 25, 2018.
7. Keller CA, Nugent RP. Seasonal patterns in perinatal mortality and preterm delivery. *Am J Epidemiol*. 1983;118(5):689-698. http://www.ncbi.nlm.nih.gov/pubmed/6637995. Accessed January 25, 2018.
8. Cooperstock M, Wolfe RA. SEASONALITY OF PRETERM BIRTH IN THE COLLABORATIVE PERINATAL PROJECT: DEMOGRAPHIC FACTORS. *Am J or Epidemiol*. 124(2). http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.829.8841&rep=rep1&type=pdf. Accessed January 25, 2018.
9. Kalkstein LS, Greene JS. An evaluation of climate/mortality relationships in large U.S. cities and the possible impacts of a climate change. *Environ Health Perspect*. 1997;105(1):84-93. http://www.ncbi.nlm.nih.gov/pubmed/9074886. Accessed January 25, 2018.
10. McGeehin MA, Mirabelli M. The potential impacts of climate variability and change on temperature-related morbidity and mortality in the United States. *Environ Health Perspect*. 2001;109 Suppl 2:185-189. http://www.ncbi.nlm.nih.gov/pubmed/11359685. Accessed January 25, 2018.
11. McMichael AJ. Globalization, Climate Change, and Human Health. *N Engl J Med*. 2013;368(14):1335-1343. doi:10.1056/NEJMra1109341.
12. Franchini M, Mannucci PM. Impact on human health of climate changes. *Eur J Intern Med*. 2015;26(1):1-5. doi:10.1016/j.ejim.2014.12.008.
13. Pascual M, Dobson A. Seasonal Patterns of Infectious Diseases. *PLoS Med*. 2005;2(1):e5. doi:10.1371/journal.pmed.0020005.
14. Mirsaeidi M, Motahari H, Taghizadeh Khamesi M, Sharifi A, Campos M, Schraufnagel DE. Climate Change and Respiratory Infections. *Ann Am Thorac Soc*. 2016;13(8):1223-1230. doi:10.1513/AnnalsATS.201511-729PS.
15. Foster CL, Mould K, Reynolds P, Simonian PL, Erlandson KM. Clinical problem-solving. Sick as a dog. Solomon CG, ed. *N Engl J Med*. 2015;372(19):1845-1850. doi:10.1056/NEJMcps1411346.
16. Chadsuthi S, Modchang C, Lenbury Y, Iamsirithaworn S, Triampo W. Modeling seasonal leptospirosis transmission and its association with rainfall and temperature in Thailand using time-series and ARIMAX analyses. *Asian Pac J Trop Med*. 2012;5(7):539-546. doi:10.1016/S1995-7645(12)60095-9.
17. De Sousa R, Luz T, Parreira P, Santos-Silva M, Bacellar F. Boutonneuse fever and climate variability. *Ann N Y Acad Sci*. 2006;1078:162-169. doi:10.1196/annals.1374.029.
18. CDC Online Newsroom | Press Release | CDC provides estimate of Americans diagnosed with Lyme disease each year. https://www.cdc.gov/media/releases/2013/p0819-lyme-disease.html. Accessed February 7, 2018.
19. González C, Wang O, Strutz SE, González-Salazar C, Sánchez-Cordero V, Sarkar S. Climate Change and Risk of Leishmaniasis in North America: Predictions from Ecological Niche Models of Vector and Reservoir Species. Galvani AP, ed. *PLoS Negl Trop Dis*. 2010;4(1):e585. doi:10.1371/journal.pntd.0000585.
20. Kaffenberger BH, Shetlar D, Norton SA, Rosenbach M. The effect of climate change on skin disease in North America. *J Am Acad Dermatol*. 2017;76(1):140-147. doi:10.1016/j.jaad.2016.08.014.
21. Bouma MJ, Dye C. Cycles of malaria associated with El Niño in Venezuela. *JAMA*. 1997;278(21):1772-1774. http://www.ncbi.nlm.nih.gov/pubmed/9388155. Accessed January 25, 2018.
22. Bouma MJ, Poveda G, Rojas W, et al. Predicting high-risk years for malaria in Colombia using parameters of El Niño Southern Oscillation. *Trop Med Int Health*. 1997;2(12):1122-1127. http://www.ncbi.nlm.nih.gov/pubmed/9438466. Accessed January 25, 2018.
23. Bouma MJ, van der Kaay HJ. The El Niño Southern Oscillation and the historic malaria epidemics on the Indian subcontinent and Sri Lanka: an early warning system for future epidemics? *Trop Med Int Health*. 1996;1(1):86-96. http://www.ncbi.nlm.nih.gov/pubmed/8673827. Accessed January 25, 2018.
24. Hales S, Weinstein P, Woodward A. Dengue fever epidemics in the South Pacific: driven by El Nino Southern Oscillation? *Lancet*. 1996;348(9042):1664-1665. doi:10.1016/S0140-6736(05)65737-6.
25. Grazzini G, Liumbruno GM, Pupella S, et al. West Nile virus in Italy: a further threat to blood safety, a further challenge to the blood system. *Blood Transfus*. 2008;6(4):235-237. http://www.ncbi.nlm.nih.gov/pubmed/19112739. Accessed January 25, 2018.
26. Liu W, Ji H, Shan J, et al. Spatiotemporal Dynamics of Hand-Foot-Mouth Disease and Its Relationship with Meteorological Factors in Jiangsu Province, China. Jin X, ed. *PLoS One*. 2015;10(6):e0131311. doi:10.1371/journal.pone.0131311.

27. Habib RR, Zein K El, Ghanawi J. Climate change and health research in the Eastern Mediterranean Region. *Ecohealth*. 2010;7(2):156-175. doi:10.1007/s10393-010-0330-1.
28. Balato N, Megna M, Ayala F, Balato A, Napolitano M, Patruno C. Effects of climate changes on skin diseases. *Expert Rev Anti Infect Ther*. 2014;12(2):171-181. doi:10.1586/14787210.2014.875855.
29. D'Amato G, Vitale C, Lanza M, Molino A, D'Amato M. Climate change, air pollution, and allergic respiratory diseases. *Curr Opin Allergy Clin Immunol*. 2016;16(5):434-440. doi:10.1097/ACI.0000000000000301.
30. Review of the National Ambient Air Quality Standards for Ozone: Policy Assessment of Scientific and Technical Information OAQPS Staff Paper. https://www3.epa.gov/ttn/naaqs/standards/ozone/data/2007_07_ozone_staff_paper.pdf. Accessed January 25, 2018.
31. Spickett JT, Brown HL, Rumchev K. Climate change and air quality: the potential impact on health. *Asia-Pacific J public Heal*. 2011;23(2 Suppl):37S-45. doi:10.1177/1010539511398114.
32. Bhaskaran K, Armstrong B, Hajat S, Haines A, Wilkinson P, Smeeth L. Heat and risk of myocardial infarction: hourly level case-crossover analysis of MINAP database. *BMJ*. 2012;345(dec13 2):e8050-e8050. doi:10.1136/bmj.e8050.
33. Bhaskaran K, Hajat S, Haines A, Herrett E, Wilkinson P, Smeeth L. Effects of ambient temperature on the incidence of myocardial infarction. *Heart*. 2009;95(21):1760-1769. doi:10.1136/hrt.2009.175000.
34. Urbach F. Ultraviolet radiation and skin cancer of humans. *J Photochem Photobiol B Biol*. 1997;40(1):3-7. doi:10.1016/S1011-1344(97)00029-8.
35. Diffey B. Climate change, ozone depletion and the impact on ultraviolet exposure of human skin. *Phys Med Biol*. 2004;49(1):R1-R11. doi:10.1088/0031-9155/49/1/R01.
36. van der Leun JC, de Gruijl FR. Climate change and skin cancer. *Photochem Photobiol Sci*. 2002;1(5):324-326. doi:10.1039/b201025a.
37. Dobbinson S, Wakefield M, Hill D, et al. Prevalence and determinants of Australian adolescents' and adults' weekend sun protection and sunburn, summer 2003-2004. *J Am Acad Dermatol*. 2008;59(4):602-614. doi:10.1016/j.jaad.2008.06.011.
38. Brotz L, Cheung WWL, Kleisner K, Pakhomov E, Pauly D. Increasing jellyfish populations: trends in Large Marine Ecosystems. In: *Jellyfish Blooms IV*. Vol Dordrecht: Springer Netherlands; 2012:3-20. doi:10.1007/978-94-007-5316-7_2.
39. Schwartz BS, Parker C, Glass TA, Hu H. Global environmental change: what can health care providers and the environmental health community do about it now? *Environ Health Perspect*. 2006;114(12):1807-1812. http://www.ncbi.nlm.nih.gov/pubmed/17185267. Accessed January 25, 2018.

Case Report

Gastrointestinal metastasis of infiltrating lobular carcinoma of the breast: Four case reports and literature review

Belma Doyle, Andrew Palmier, Stephanie Magri, Gordon Caruana-Dingli, Michelle Ceci

Abstract

Breast cancer is the most common cancer in women worldwide. The two main types of invasive breast cancer are invasive ductal and invasive lobular carcinoma. The most common sites of breast cancer metastasis encountered are liver, lung, bone and brain. Metastasis of primary lobular breast carcinoma to gastrointestinal (GI) tract is a well-known yet rare occurrence with reported incidence ranging from 2% to 18%. We report four such cases of invasive lobular breast carcinoma metastasizing to the GI tract, and review the literature.

Belma Doyle, M.D, F.E.B.S *
RS, General Surgery Department
Mater Dei Hospital
Msida, Malta
belma@mcmadd.net

Andrew Palmier, M.D (Melit.)
BST, Opthalmology
Mater Dei Hospital
Msida, Malta

Stephanie Magri, M.D (Melit.)
Medical Doctor
Mater Dei Hospital
Msida, Malta

Gordon Caruana-Dingli, M.D, FRCS (Ed/Glas)
Consultant General and Breast Surgery
Mater Dei Hospital
Msida, Malta

Michelle Ceci, MD (Melit.)
HST, Histopathology
Mater Dei Hospital,
Msida, Malta

**Corresponding Author*

Keywords

Invasive lobular carcinoma, Breast Cancer, Gastrointestinal (GI) metastasis, Linitis plastica, E-Cadherin, Estrogen receptor (ER), Progesterone receptor (PR), CK7

Introduction

Breast cancer is the most common cancer in women worldwide. According to the Global Health Estimates, World Health Organization 2013, breast cancer was responsible for over 508 000 deaths in 2011. Women in Western Europe saw greater incidence of breast cancer, 89.7 per 100,000, when compared to women in Eastern Africa where the incidence of breast cancer was 19.3 per 100,000.[1]

The two main types of invasive breast cancer are invasive ductal carcinoma comprising 80% of invasive breast cancers, and invasive lobular carcinoma accounting for about 10%.[2] Most commonly breast cancer is known to metastasize to the liver, lung, bone and brain. In addition to these common sites, the propensity of invasive lobular carcinoma to metastasize to extra hepatic gastrointestinal (GI) sites, peritoneum, and adnexae has been well reported in the literature.[3-6,11] Despite this, metastasis of primary lobular breast carcinoma to GI tract is a rare occurrence, with reported incidence ranging from 0.7% to 18%. The stomach is the most commonly affected organ and metastasis here most often presents as linitis plastica.[3,4,8,10,12,19] The finding of GI tract metastasis as the first presentation of breast carcinoma is particularly uncommon, but does occur.[3] We report four cases of primary breast carcinoma metastasizing to GI tract, with one of the patients being diagnosed with primary breast cancer and GI metastasis synchronously. Our patients experienced a wide range of gastrointestinal symptoms varying from vague discomfort and loss of appetite to severe abdominal pain, nausea and vomiting.

Case Presentations

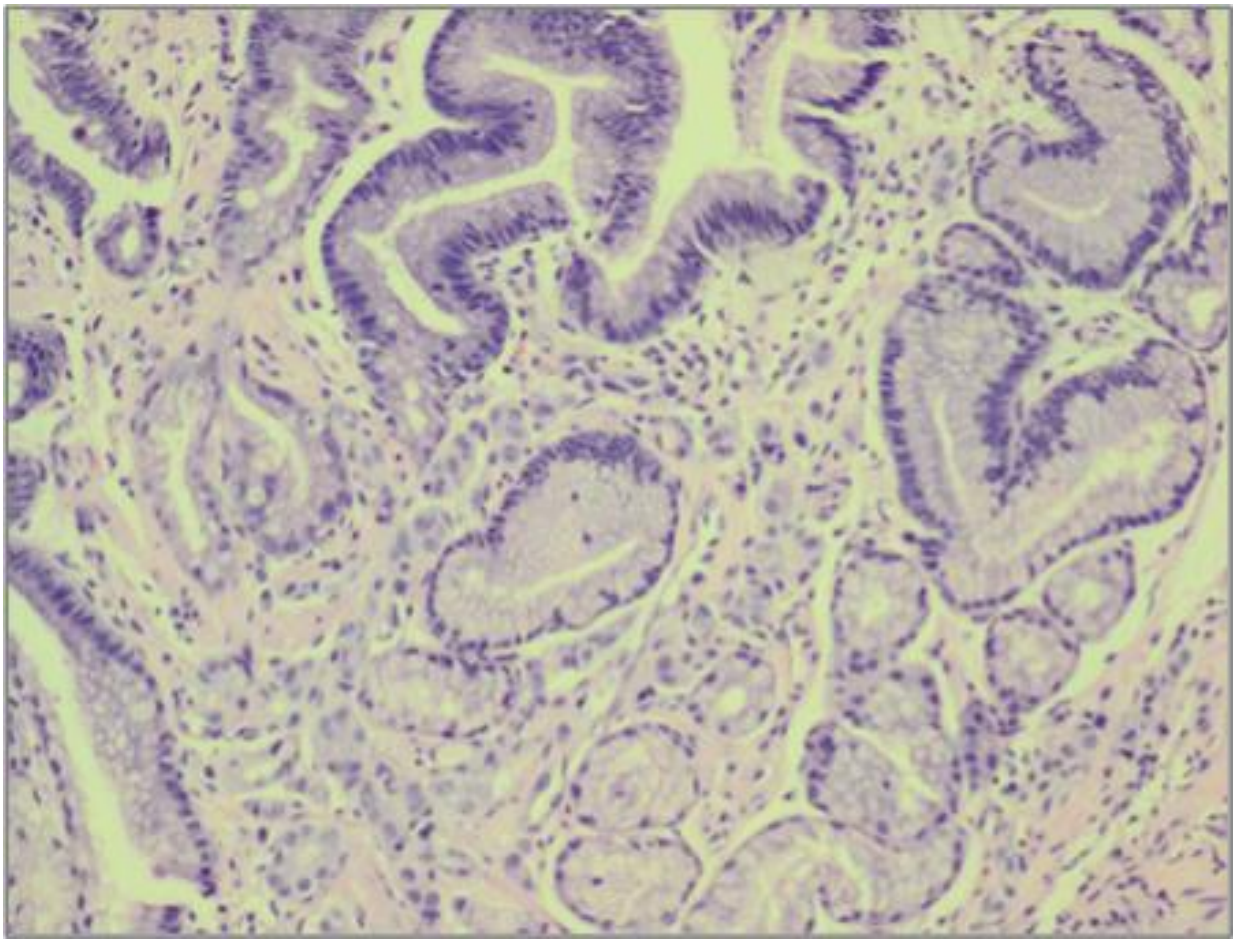
Case presentation 1

A 67-year-old female presented to our outpatient clinic in view of severe weight loss and loss of appetite. No other associated symptoms were reported. On physical examination she was found to have a palpable, non-tender epigastric mass, accompanied by left breast deformity with an underlying breast lump. When questioned further, it transpired that the left breast mass had been present for 20 years, during which she never sought medical attention. CT study revealed small ill defined hypodense lesions in the liver due to possible metastasis, thickening of the wall of the stomach a 17 mm round lesion between stomach, splenic vein and spleen, and rectal wall thickening accompanied by pelvic ascites. Also of note was the finding of collapsed of sixth thoracic vertebra and irregular bone texture of thoracic vertebrae 5 and 11 and the second lumbar vertebra.

OGD confirmed the CT results noting a thick, rigid stomach wall suggestive of linitis plastica extending from the oesophaghogastric junction (OGJ) to the pylorus. Biopsy of the breast mass revealed invasive lobular carcinoma grade II, estrogen receptor (ER) and progesterone receptor (PR) positive and Her 2 and E-cadherin negative Endoscopic biopsy demonstrated metastatic mammary lobular carcinoma expressing cytokeratin 7 (CK7) and ER receptors, with cytokeratin 20 (CK20), the homeobox intestinal differentiation factor CDX2, and E-Cadherin negative (Figure 1). The rectal thickening found on the CT scan was suggestive of metastasis to the rectum, however this was not confirmed by biopsy due to patient's unwillingness to undergo the procedure.

The patient was referred to oncology and chemotherapy was initiated.

Figure. 1: *Stomach biopsy specimen stained with H&E, showing extensive infiltration of the lamina propria by malignant decohesive epithelial cells, consistent with metastatic mammary lobular carcinoma.*

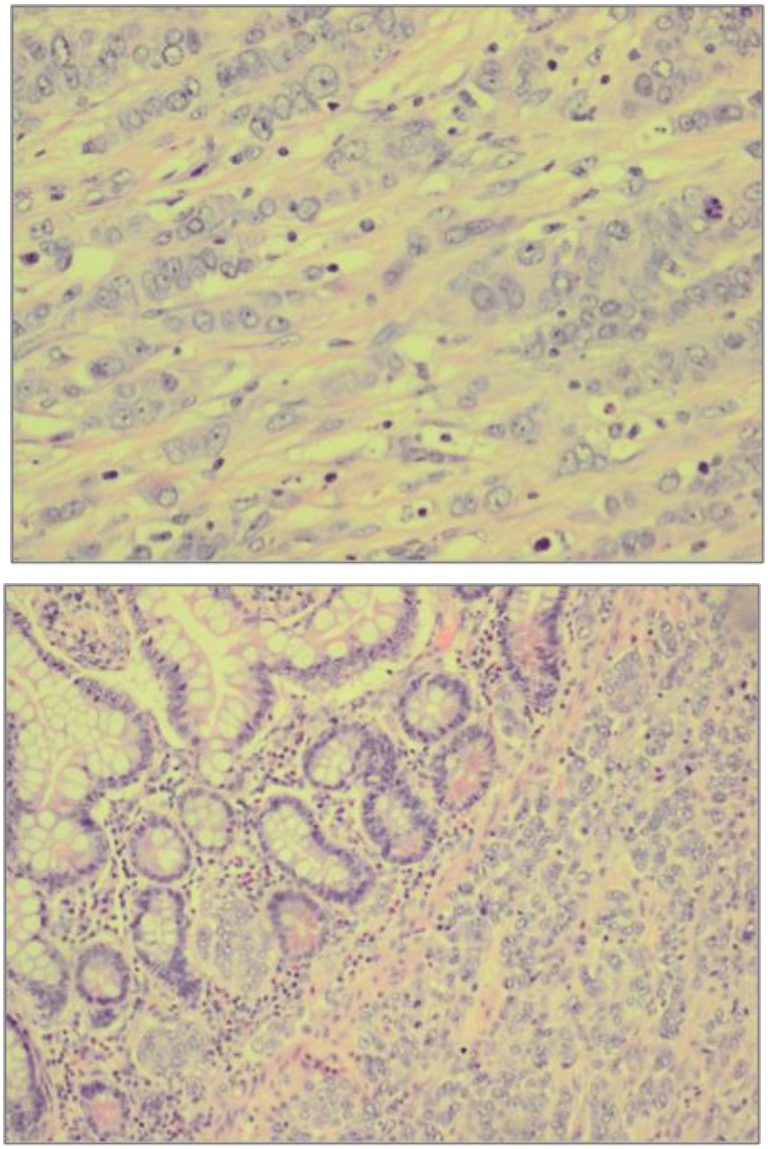


Case Presentation 2

A 56 year old female presented to the outpatient clinic with a five-day history of constipation, colicky abdominal pain, nausea and vomiting. Nine years prior to this presentation the patient had undergone a wide local excision and axillary clearance for a left breast lump. Postoperative histology showed invasive lobular carcinoma, grade II, ER positive with no metastasis to axillary lymph nodes. She was subsequently treated with radiotherapy to the left breast and five-year course of Tamoxifen. Seven years later patient was diagnosed with regional metastases and treated with radiotherapy to cervical, pectoral and internal mammary regions followed by a course of chemotherapy.

CT scan of abdomen and pelvis showed multiple dilated ileal loops with a transition point in the distal ileum and a moderate amount of ascites. At laparotomy small bowel stricture was identified and resected together with a peritoneal nodule. Histological sections from small intestine confirmed diffuse infiltration by a grade III invasive lobular carcinoma (Figures 2a and 2b), which involved the whole thickness of the intestinal wall with widespread vascular and perineural invasion and lymph nod metastasis. The peritoneal nodules examined revealed the presence of metastatic lobular carcinoma. The tumor was found to be ER, PR, Her2 and E-cadherin negative. The patient underwent chemotherapy treatment.

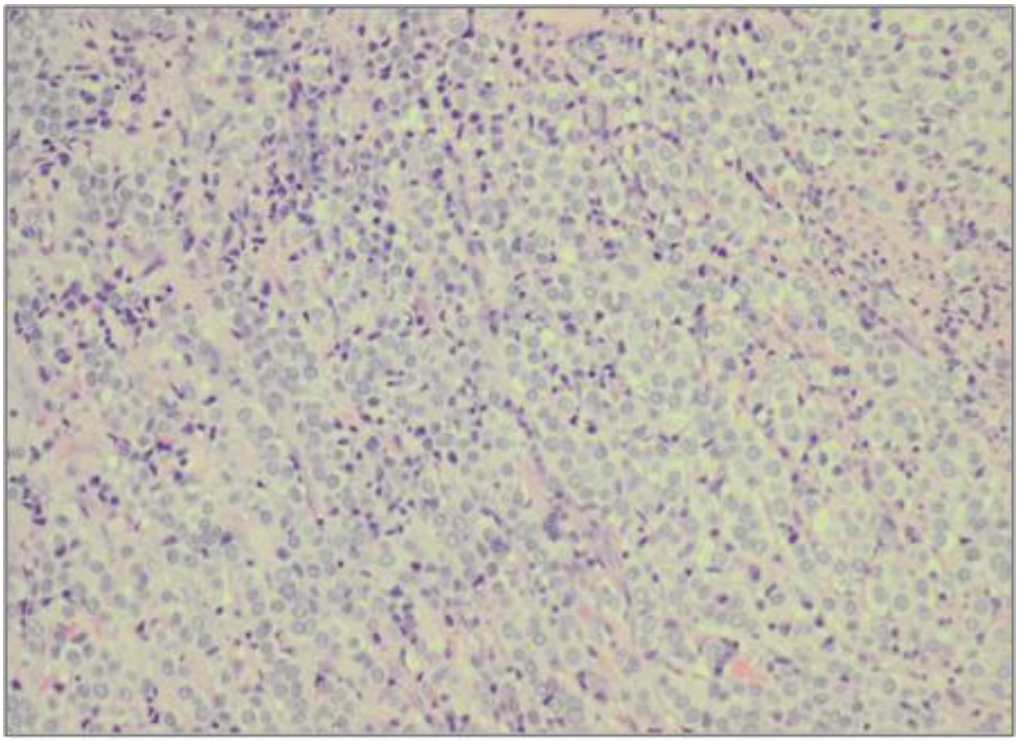
Figures 2a and 2b: *Sections from the small intestine stained with H&E, showing diffuse infiltration by grade III invasive lobular carcinoma involving the whole thickness of the intestinal wall.*



Case presentation 3

An 88-year-old female presented to the outpatient clinic in view of large (8x5x3.5cm), firm, and mobile mass in the right axilla associated with right nipple retraction. Right axillary excisional biopsy was preformed, which showed ER positive, infiltrating metastatic adenocarcinoma from a primary breast carcinoma. The patient underwent radiotherapy to the right breast and axilla, and hormonal treatment of Tamoxifen was initiated with good response. Follow up radiological studies revealed no spread and no distant metastases. Eleven years later the patient presented to the Emergency Department with persistent nausea and vomiting. Upper GI follow through showed an obstructing stricture in the distal duodenum and duodeno-jejunal flexure. Exploratory laparotomy showed a tumour obstructing the small bowel at the duodeno-jejunal flexure, para-aortic lymphadenopahy and deposits on anti-mesenteric border of jejunum. Biopsy of the stricture was taken, and gastrojejunostomy fashioned. Histology revealed metastatic lobular breast carcinoma to GI tract (Figure 3).

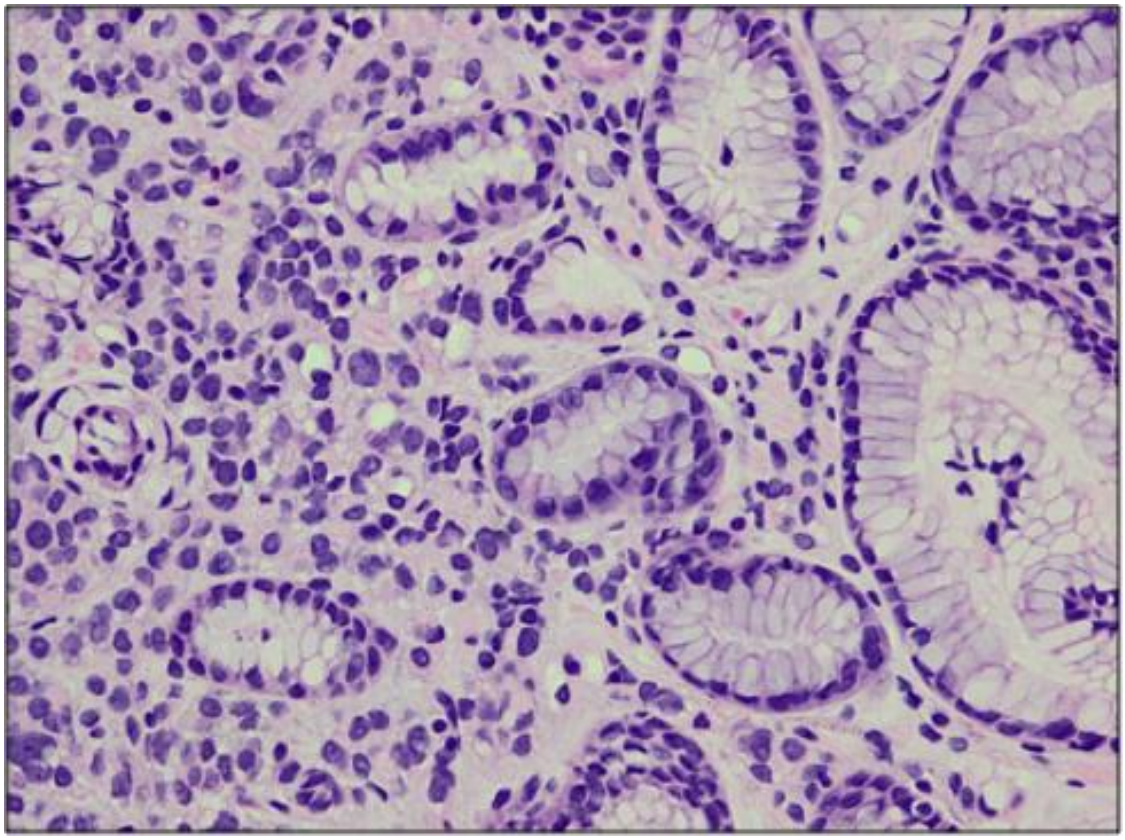
Figure 3: *Histology specimen from the duodeno-jejunal flexure stained with H&E, showing metastatic adenocarcinoma from breast primary. Tumour cells can be seen in the bowel mucosa surrounded by inflammatory cells.*



Case Presentation 4

A 52 year old female with a history of right mastectomy with axillary clearance for invasive lobular cancer metastasizing to 6 out of 29 axillary lymph nodes 6 years prior, presented with epigastric discomfort and 20 kg weight loss in 3 months. In view of her history and raised Ca 125, a CT scan of thorax, abdomen and pelvis were preformed which demonstrated an irregularity at the gastroesophageal junction and edema of the wall of the stomach with free pelvic fluid. Multiple osteolytic bone lesions were also noted in the spine and pelvis. Oesophagogastroduodenoscopy (OGD) and endoscopic gastric cardia biopsies were carried out. The histology confirmed metastatic lobular breast carcinoma ER, HER2, cytokeratin 7 (CK7) and gross cystic disease fluid protein 15 (GCDFP-15) positive, and PR, cytokeratin 20 (CK20), lymphocyte common antigen CD45, and E-cadherin negative (Figure 4). Cytology of free peritoneal fluid during the staging laparoscopy demonstrated adenocarcinoma. The patient was referred to oncology for further treatment.

Figure 4: *Gastric cardia biopsies. Neoplastic cells infiltrating lamina propria, arranged in trabecules and single-cell lines as shown. Atypical epithelial cells are ER and HER2 positive.*



Discussion

The expected site of breast cancer metastasis commonly includes lung, liver, bone and brain. However, invasive breast carcinoma of lobular pathology, in addition to metastasizing to the listed sites, also has a propensity to metastasize to unusual areas such as GI tract, peritoneum and adnexa.[6] This difference in metastatic pattern of lobular and ductal carcinoma was demonstrated by Borst et al. who analyzed the rates of metastasis of invasive lobular vs. invasive ductal carcinoma and were able to show that rate of metastasis to the gastrointestinal tract (4.5% *vs* 0.2%), gynecologic organs (4.5% *vs* 0.8%), peritoneum-retroperitoneum (3.1% *vs* 0.6%), adrenal glands (0.6% vs 0%), bone-marrow (21.2% *vs* 14.4%), and lung-pleura (2.5% *vs* 10.2%) were significantly different ($p<0.05$).[21] The time interval from diagnosis of primary breast cancer to metastasis to GI is up to 30 years.[14]

The reported incidence of invasive lobular carcinoma metastasis to GI tract ranges from 0.7-18%.[8,12] The stomach seems to be the most common site of metastasis. During the year 2000, Taal et al. retrospectively evaluated 51 patients with metastatic gastric carcinoma and found that 83% of patients with gastric involvement had lobular breast cancer as a primary histological subtype.[16] Similar findings were observed by Almubarak *et al.* who completed a single institution retrospective study of 35 patients with metastatic breast carcinoma to the stomach and found that 97% of the gastric metastasis from a breast cancer was derived from invasive lobular carcinoma. In lobular breast carcinoma, gastric metastasis most often presents as linitis plastica, while metastatic ductal breast carcinoma exhibits a nodular pattern.[4,8,10]

What gives metastatic linitis plastica its appearance is a diffuse infiltration of gastric wall by poorly differentiated tumor cells, resulting in reactive fibrosis.[9] As in our case, metastatic linitis plastica is usually diagnosed by endoscopy and endoscopic biopsy, although CT plays an important role in diagnosing metastases beyond the stomach. Endoscopic findings may present in 3 different patterns: localized lesions (18%), diffuse infiltration (57%), and external compression at the cardia or pylorus (25%).[16] When taking a biopsy during endoscopic procedures it is important to take deep

biopsies due to the observation that diffuse infiltration is predominantly seen within the submucosa and muscularis propria.[9]

The differentiation between the primary breast cancer metastasis to GI tract and primary gastric cancer is of upmost importance, as the treatment options will differ greatly. It may be difficult to distinguish between primary and metastatic lesions using only histology. In some cases metastasis of lobular breast carcinoma mimics primary gastric adenocarcinoma by producing signet ring morphology, making it almost indistinguishable from primary gastric linitis plastica. Therefore, immunohistochemistry can be of great help in determining the accurate diagnosis.[18]

Symptoms elicited by metastasis to GI tract are variable ranging from vague abdominal discomfort to acute GI symptoms. Symptoms encountered most often are weight loss, early satiety, nausea, vomiting and abdominal pain, however, incidental finding of metastases in asymptomatic patients is also common.[7,11] Taal *et al*. in review of 51 patients found that most common presentation was anorexia (71%), followed by epigastric pain (53%), and vomiting (41%).[16]

Metastasis to the GI tract from invasive carcinoma of the breast represents evidence of systemic disease and as such it is primarily treated with chemotherapy, hormonal therapy or combination of the two. A partial remission with a clear palliative effect was demonstrated in only 46% of patients receiving systemic therapy with no obvious difference in response rates between hormonal treatment and chemotherapy. Surgical intervention is reserved for complications such as bleeding or obstruction.[15-16,18] The choice of treatment depends on the presenting symptoms, age, general condition, receptor status, and previous systemic treatments.[20] Advanced age at diagnosis and gastric metastases has a negative effect on survival, whereas treatment with systemic chemotherapy or Tamoxifen carries a positive effect on survival.[19] McLemore *et al* reported that surgical intervention did not have a significant effect on survival (28 vs. 26 months).[19] Some survival benefit was seen in a select group of patients with metastasis only to the GI tract that underwent palliative surgical resection. Surgical intervention should be reserved for palliation, or may be a reasonable choice in cases of solitary resectable GI tract metastases. Appropriate systemic treatment for metastatic breast carcinoma is the preferred treatment.

The reported median survival of patients undergoing systemic treatment for metastatic breast cancer to the stomach and gastrointestinal tract varied between 10 and 28 months.[17,29,22]

Conclusion

When a patient with a history of breast cancer presents with gastrointestinal symptoms, or an apparent primary gastric cancer is diagnosed, a high index of suspicion for a potential breast cancer metastasis has to be maintained. The differentiation between breast cancer metastasis from primary gastric cancer is of upmost importance, as the treatment options of the two differ greatly. Furthermore, increased awareness of the possibility of breast cancer metastasis should be observed in females without history of breast cancer who are diagnosed with diffuse-type gastric cancer or gastrointestinal carcinoma of unknown origin.

Reference

1. who.int [internet]. World Health Organization. Breast cancer: prevention and control; c2016 [cited 2016 May 29]. Available from: http://www.who.int/cancer/detection/breastcancer/en/
2. cancer.org [internet]. American Cancer Society. Types of breast cancers; c2016 [cited 2016 Apr 5]. Available from: https://www.cancer.org
3. Abid A, Moffa C, Monga DK. Breast cancer metastasis to the GI tract may mimic primary gastric cancer. J Clin Oncol. 2013;31(7):e106-7.
4. Cormier WJ, Gaffey TA, Welch JM, Welch JS, Edmonson JH. Linitis plastica caused by metastatic lobular carcinoma of the breast. Mayo Clin Proc. 1980;55(12):747-53.
5. Carcoforo P, Raiji MT, Langan RC, Lansara S, Portinari M, Maestroni U, et al. Infiltrating Lobular Carcinoma of the Breast Presenting as Gastrointestinal Obstruction: A Mini Review. J Cancer. 2012; 3: 328-32.
6. Winston CB, Hadar O, Teitcher JB, Caravelli JF, Sklarin NT, Panicek DM, et al. Metastatic lobular carcinoma of the breast: patterns of spread in the chest, abdomen, and pelvis on CT. AJR Am J Roentgenol. 2000;175(3):795-800.
7. Switzer N, Lim A, Du L, Al-Sairafi R, Tonkin K, Shiller D. Case series of 21 patients with extra-hepatic metastatic lobular breast carcinoma to the gastrointestinal tract. Cancer Treatment Communications. 2015;3:37-43.
8. Whitty LA, Crawford DL, Woodland JH, Patel JC, Nattier B, Thomas CR Jr. Metastatic breast cancer presenting as linitis plastica of the stomach. Gastric Cancer. 2005;8(3):193-7.

9. Kodera Y, Nakanishi H, Ito S, Mochizuki Y, Yamamura Y, Fujiwara M, et al. Detection of disseminated cancer cells in linitis plastica-type gastric carcinoma. Jpn J Clin Oncol. 2004;34(9):525–31.
10. Rusticeanu M, Schuster M, Moga SL, Solomayer EF, Bohle RM, Lammert F, et al. Metastatic lobular breast cancer presenting as gastric linitis plastica. Am J Med. 2011;124(7)e5-6.
11. Ferri LE, Onerheim R, Emond C. Linitis plastica as the first indication of metastatic lobular carcinoma of the breast: case report and literature review. Can J Surg. 1999 Dec;42(6):466-9.
12. Arrangoiz R, Papavasiliou P, Dushkin H, Farma JM. Case report and literature review: metastatic lobular carcinoma of the breast an unusual presentation. Int J Surg Case Rep. 2011; 2(8): 301–5.
13. globocan.iarc.fr. International Agency for Research on Cancer (IARC) and World Health Organization (WHO). GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012; c2014 [cited 2016 Apr 6]. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
14. Benfiguig A, Anciaux ML, Eugene CL, Benkémoun G, Etienne JC. Gastric metastasis of breast cancer occurring after a cancer-free interval of 30 years. Ann Gastroentetol Hepatol. 1992;28:175–7.
15. Schwarz R, Klimstra D, Turnbull A. Metastatic breast cancer masquerading as gastrointestinal primary. Am J Gastroenterol. 1998;93:111–4.
16. Taal BG, Peterse H, Boot H. Clinical presentation, endoscopic features, and treatment of gastric metastases from breast carcinoma. Cancer. 2000;89: 2214-21.
17. Almubarak MM, Laé M, Cacheux W, De Cremoux P, Pierga J, Reyal F, et al. Gastric metastasis of breast cancer: A single centre retrospective study. Dig Liver Dis. 2011;43(10):823-7.
18. Pectasides D, Psyrri A, Pliarchopoulou K, Floros T, Papaxoinis G, Skondra M, et al. Gastric metastases originating from breast cancer: report of 8 cases and review of the literature. Anticancer Res. 2009;29(11):4759-63.
19. McLemore EC, Pockaj BA, Reynolds C, Gray RJ, Hernandez JL, Grant CS, et al. Breast cancer: presentation and intervention in women with gastrointestinal metastasis and carcinomatosis. Ann Surg Oncol. 2005;12:886-94.
20. Jones GE, Strauss DC, Forshaw MJ, Deere H, Mahedeva U, Mason RC. Breast cancer metastasis to the stomach may mimic primary gastric cancer: report of two cases and review of literature. World J Surg Oncol. 2007;5: 75.
21. Borst MJ, Ingold JA. Metastatic patterns of invasive lobular versus invasive ductal carcinoma of the breast. Surgery. 1993 Oct;114(4):637-42
22. O'Connell FP, Wang HH, Odze RD. Utility of immunohistochemistry in distinguishing primary adenocarcinomas from metastatic breast carcinomas in the gastrointestinal tract. Arch Pathol Lab Med. 2005;129:338-47.

Atypical presentation of a Rib Chondrosarcoma

Samuel Zahra, Kevin Schembri

Abstract

Background: This case report represents a variation from the typical characteristics of an uncommon cardiothoracic pathology, i.e rib chondrosarcomas. Usually this pathology is seen in patients over 40 years of age and grows relatively slowly, taking around 2 years to present clinically.

Case Presentation: Our patient was an asymptomatic and healthy 27 year old male who presented with a large right sided thoracic mass. CT (Computed Tomography) scaning revealed an inhomogeneous lesion around 6cm in diameter, arising from the 8th right rib, with no obvious signs of aggressive type of growth and no evidence of metastatic spread. The decision was taken to excise the lesion based on clinical and radiological evidence. Histopathological analysis was carried out at two centres and reported a Grade II 55mm x 48mm x 43mm show with a variably cellular tumour consistent with chondrosarcoma. The case was discussed with the oncological team who advised no need for further treatment given histology and radiological report, except clinical and radiological surveillance.

Conclusions: Chondrosarcomas are the 3rd commonest type of bone tumour however it is considered rare for them to originate from the ribcage in a young individual over a relatively short time span. CT scanning is considered the gold standard image and surgery as the main form of management.

Samuel Zahra MD, MRCS (Irel).*
Department of Cardiothoracic Surgery,
Mater Dei Hospital,
Msida, Malta
samuelzahra13@gmail.com samuel.zahra@gov.mt

Kevin (KS) Schembri MD, AFRCS, FETCA, MA,
Cardiothoracic Surgeon,
CEO Mental Health Malta
Department of Cardiothoracic Surgery,
Mater Dei Hospital,
Msida, Malta

Acknowledgment: Radiology and Pathology Departments

Corresponding Author

Keywords

rib, chondrosarcoma, cardiothoracic, oncological

Background

Chondrosarcomas represent a heterogenous group of bone tumours, common trait being the ability to produce chondroid matrix.[1] The majority of these tumours arise from the pelvis or long bones.[2-4] Malignant primary tumours of the thoracic wall account for 4.5-8% of all bone tumours with chondrosarcomas representing 40%.[5] Biological behavior varies according to site and grade.[2] CT scanning is considered to be the gold standard for diagnosis and surgical planning[1], with the commonest finding showing a low density mass with coarse calcifications[3]. We report a case of a chondrosarcoma located on the right 8th rib, in a young healthy male patient, whose only complaint was the rapidly growing mass.

Case Presentation

27 year old Caucasian patient, presented to the emergency department, complaining of a lump he noted on his right side of his chest. The lump grew from non-palpable to palpable over a timespan of 2 months. It was not painful, did not discharge and had visible punctum. No history of trauma was given and it was not affecting his daily activities.

Patient claimed he regularly smokes 2 packets of tobacco a day but did not note any worsening shortness of breath, cough, sputum, fever or weight loss.

Patient had no prior medical or surgical history. He worked in the delivery system and lived with his mother. A family history of high blood pressure and diabetes was present.

On examining the patient cardiovascular examination revealed normal heart sounds and bilateral vesicular air entry despite his smoking habits. Abdominal examination revealed a 3 finger

breath hepatomegaly but no signs of jaundice or other stigmata of hepatic pathology.

The lesion itself was found to be located on the right side of the lower chest wall. It was medial to the mid-axillary line with no obvious signs of erythema. The lump was solid in nature, non-tender and had a well defined smooth border which could be traced as originate from the 8th right rib.

Routine blood results were taken including a Full blood count and inflammatory markers- which failed to show signs of ongoing inflammatory process.

A Chest X-ray was ordered and exhibited a solid mass originating from the lower right chest wall (Figure 1). This was followed by a CT scan to get more detailed radiological information.

The CT report commented on the presence of an inhomogeneous mass about 6cm in diameter, arising form the 8th right rib with no obvious signs of aggressive type of growth. Note was also made of the mass pushing on the right liver lobe (Figure 2,3).

Our main differential was some form of rib tumour, suspecting a rib chondroma or chondrosarcoma.

Surgery

The decision was taken to remove the tumour surgically by the cardiothoracic department. This involved using a general anaesthetic to gain access to the lesion. The lesion in theatre was noted to be a well defined mass originating from the 8th right rib. It was highly vascular and there was no indication that the mass was in contact with the rib superior to it (Figure 4). Medially the mass was abutting the right liver lobe and was displacing it but again no signs of obvious liver involvement was noted. The lesion was removed together with a 4cm segment of unaffected bone medially and laterally (Figure 5).

The defect created was reinforced using non-absorbable sutures and the lesion was sent to histopathology and a chest drain was inserted.

Histology report

Macroscopic: A rib segment which measures 95mm in length and 10mm in diameter. A firm, nodular, lobulated tumour occupies the middle third of the rib. The tumour measures 55mm x 48mm x 43mm and is 27mm away from the closest surgical margin. The tumour has a diffusely homogenous chondro-myxoid cut surface.

Microscopic: Sections from the rib lesion show a variably cellular tumour composed of atypical chondrocytic cells set in a predominantly chondroid tumoural matrix. The chondrocytes exhibit mild-to-moderate nuclear pleomorphism and both binucleate and trinucleate forms are readily identified. However, no appreciable mitotic activity is present. In areas, neoplastic non-mineralised and mineralised osteoid formation is seen, in which entrapped tumour cells are present. Mucomyxoid degeneration of the stroma is visualised in areas. The tumour focally infiltrates the bone marrow (Figure6,7,8).

Diagnosis

Excision of right 8th rib tumour: Chondrosarcoma, grade 2.

Oncology

The results were then discussed with the oncological team who advised, that chemo-radiotherapy or further resections were unnecessary.

Discussion

Chondrosarcomas are considered to be very rare malignant tumours when growing from the ribs. Typically they present in an older age group, however the patient in this case was 27 years at the time of presentation.[1,6] Described as slow growing, the patients' tumour grew from clinically palpable to pre-resection size in less than 2 months.

Diagnosing rib chondrosarcomas involves a combination of clinical and radiological investigations. With respect to imaging, CT is considered to be the golden standard, even though most lesions will likely been seen on a plain chest X-ray.[6] In fact biopsy is not required prior to surgery, highlighting the importance of CT imaging to help deciding to proceed with surgical intervention as the next step.

The most effective treatment is surgical resection with a healthy surgical margin as was done in the situation of our patient[3], with adjuvant chemo/radiotherapy therapy not playing a major role

in managing these sort of tumours.[5] The outcome from surgical management for rib chondrosarcomas is more favourable when compared to chondrosarcomas originating from other sites in the body; with a 5 year mortality quoted at 10%, local recurrence at 17% and metastatic rate of 12%.[6] The oncological outcome after surgery is worse in tumors >5 cm, in tumors with positive resection margins and grade 3 chondrosarcoma.[7] The patient post procedure will require physical examination and imaging chest X-ray every 3-6 months for the first 5 years. This constitutes the final part of the management plan, surveillance and monitoring.

***Figure 1**: Lesion seen on AP CXR located in the distal portion of the right rib cage*

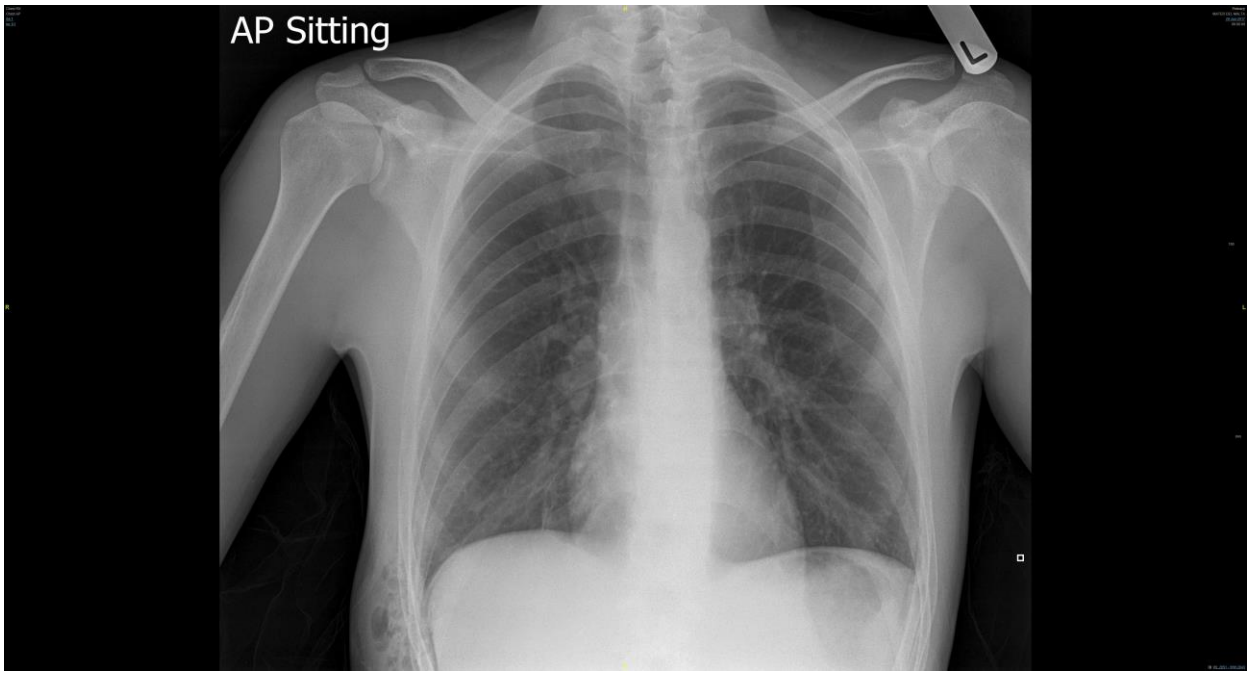


***Figure 2**: Sagittal CT scan showing lesion growing from the 8th right rib*

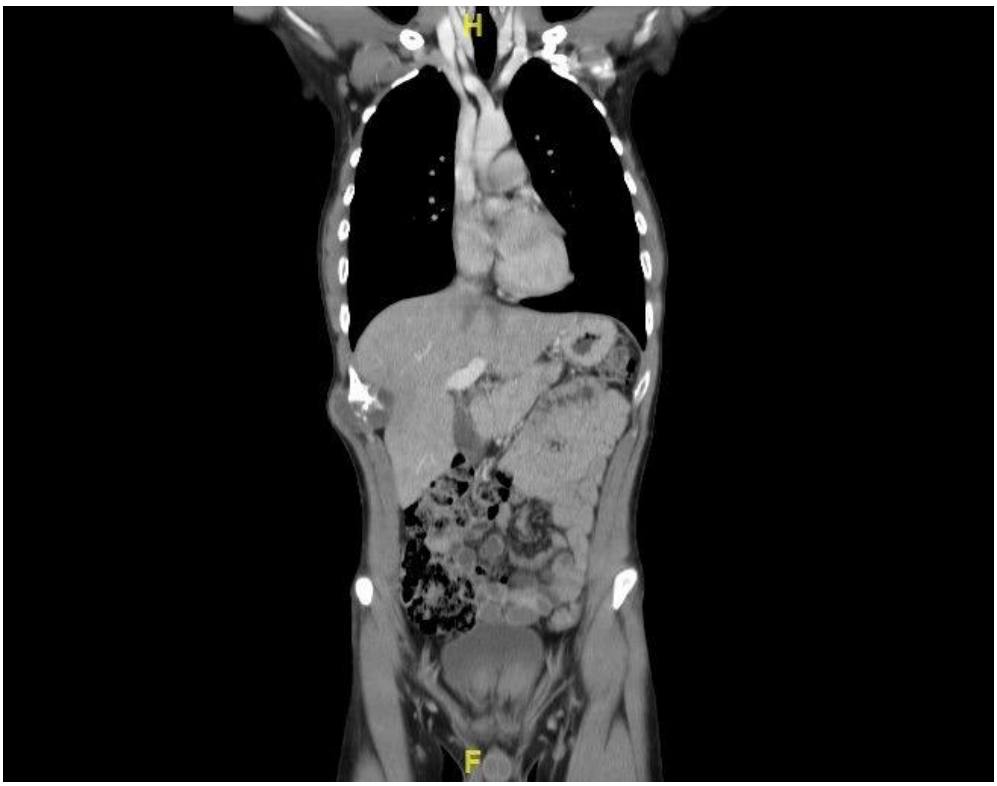


***Figure 3**: Coronal CT scan showing extent of lesion compressing the right lobe of the liver*

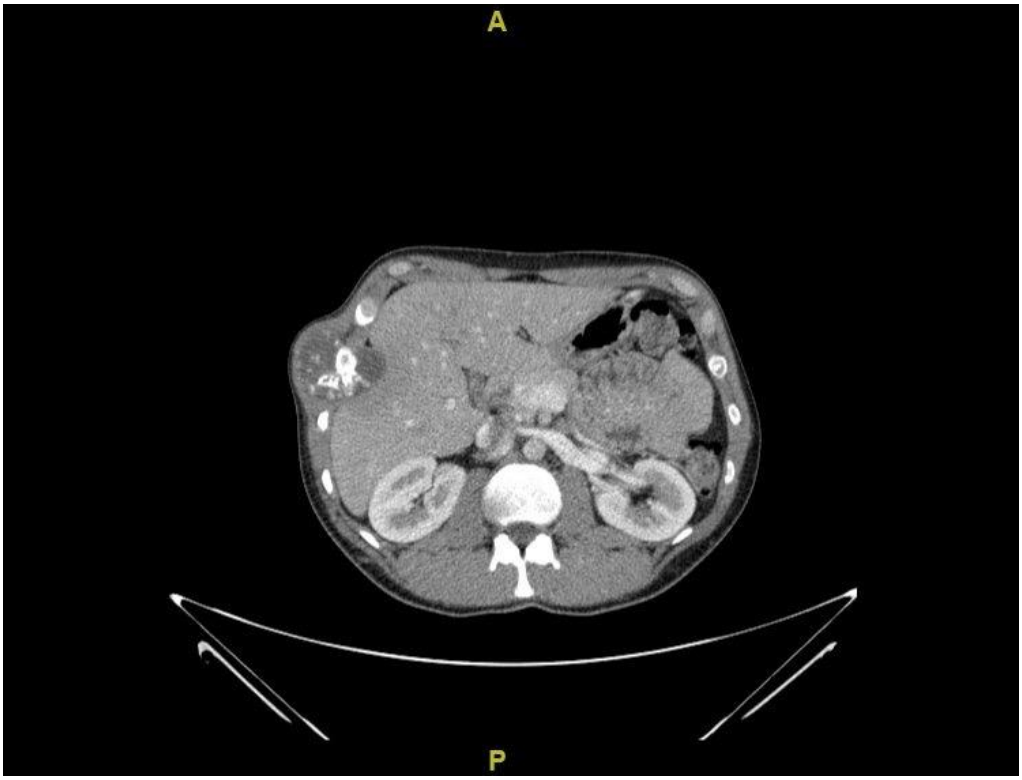


***Figure 4**: Intraoperative view of the tumour*

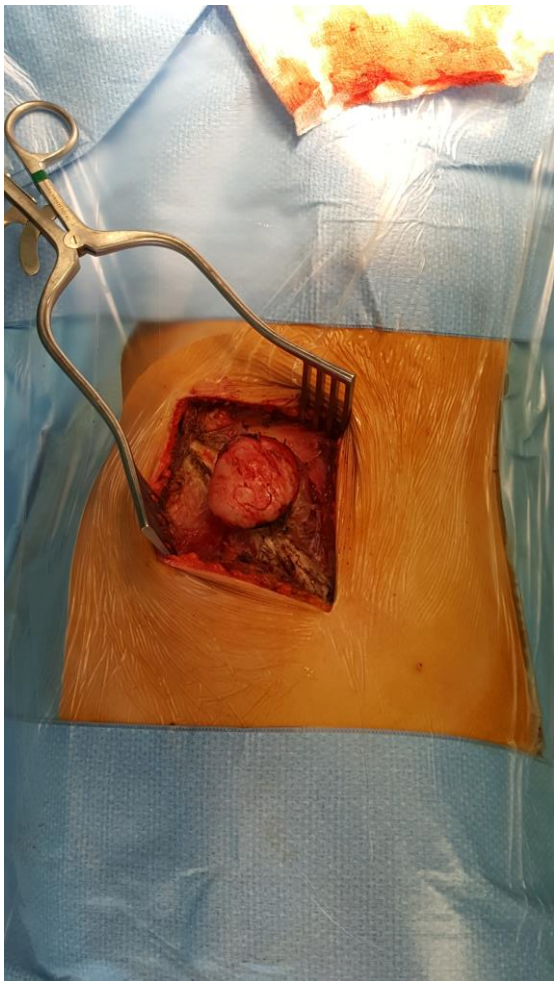


***Figure 5**: Gross histological specimen*

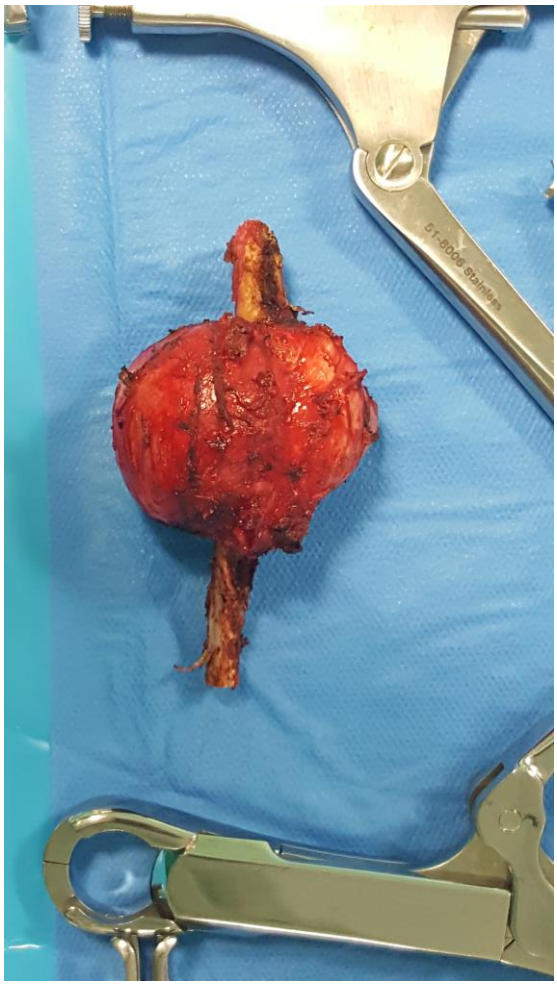


***Figure 6**: H&E stained slide at x200 magnification which demonstrates the chondroid matrix of the tumour, in which are set numerous neoplastic chondrocytes*

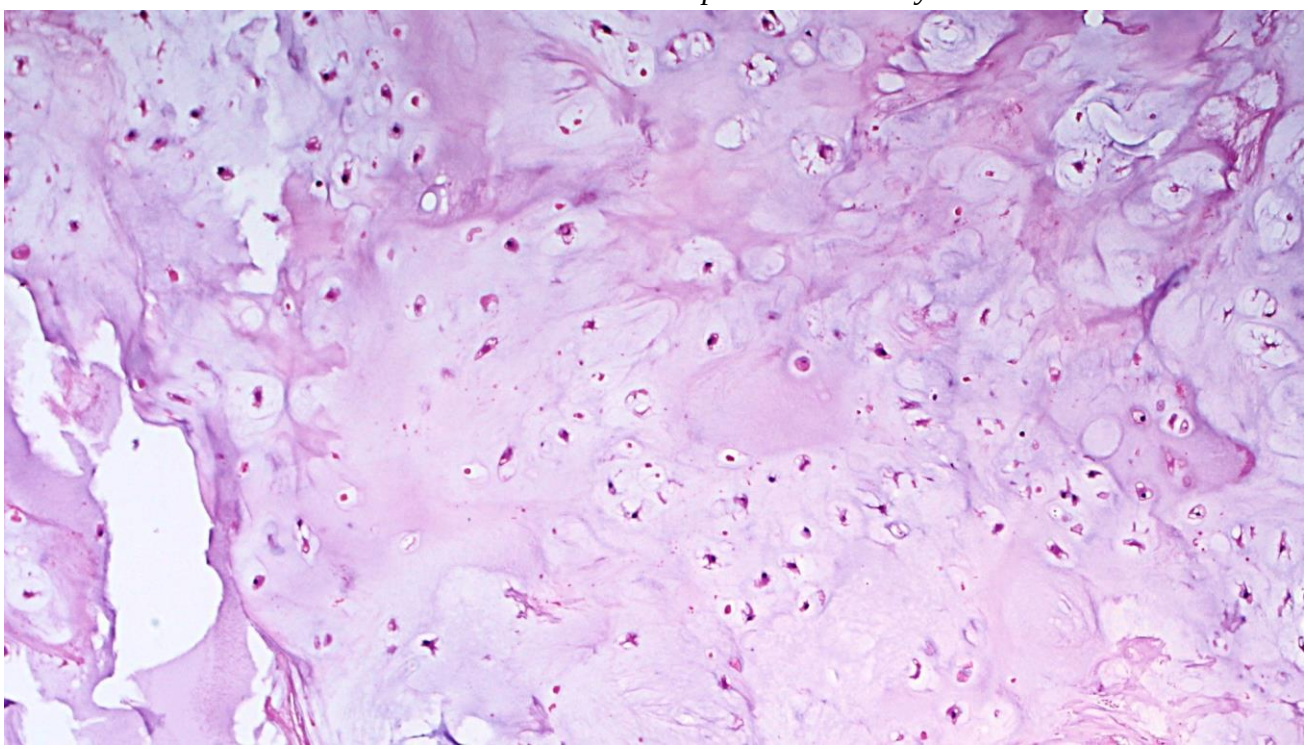


***Figure 7**: H&E stained slide at x400 magnification. The atypical nature of the chondrocytes wherein the neoplastic cells are pleomorphic, hyperchromatic and have a somewhat stellate morphology.*

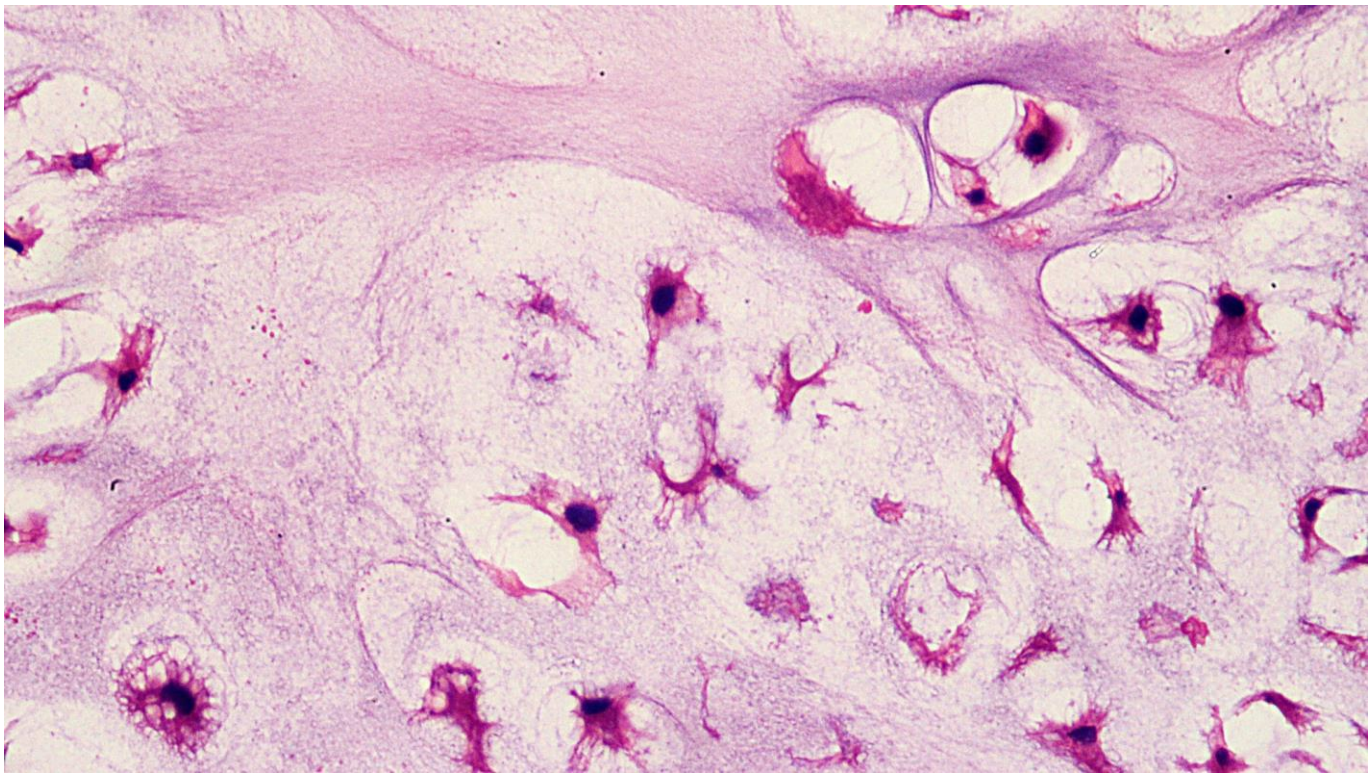
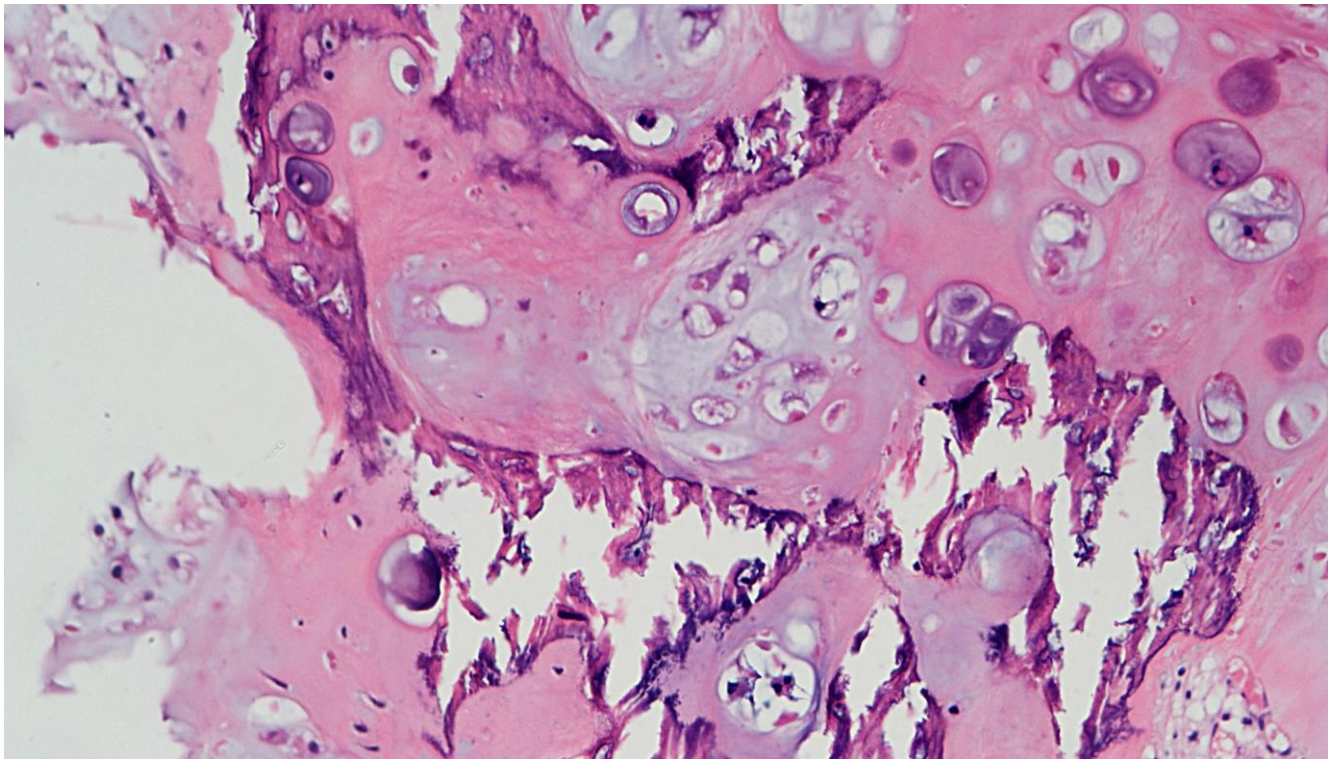


***Figure 8:** H&E stained slide at x200 magnification. Foci of calcification were also present within the tumour which, in areas, appeared somewhat ossific in nature, which is what prompted referral of the case abroad for further differentiation between chondrosarcoma (within which one is not allowed ossification from a histopathological standpoint) and chondroblastic osteosarcoma.*
This differentiation is not easy and is aided by molecular and genetic tests (eg: IDH mutations) which are not performed locally.



Conclusions

Chondrosarcoma represent a heterogeneous group of malignancies. Chondrosarcomas account for 20% of bone sarcomas, of which 3.1% arise from the chest wall and 1.8% from the rib. There is a slight male predominance with mean age 47±17.2years.[7] Surgical resection of both primary and recurrent chondrosarcoma of the rib is effective and the mainstay method of treatment.

Learning Points:

- Chondrosarcomas are the 3rd commonest type of bone tumour however it is extremely rare for them to originate from the ribcage in a young individual over a relatively short time span.
- CT scanning is considered the gold standard image and surgery as the main form of management.
- Aim is to achieve good resection margins to get R0 resection. Oncological management in the form of chemo-radiotherapy is rarely beneficial and active surveillance with progressively longer intervals form the crux of patient management.

References

1. Mima Maychet BS, Simon D. Chondrosarcoma of a rib. International Journal of Surgery Case Reports 2015;126-8.
2. Eva R, et al. Prognosis of Primary and Recurrent Chondrosarcoma of the Rib. Annals of Surgical Oncology 2016; 23:811-7.
3. Katsunari M, Mitsuhiro U, Yoshihiro M. Costal chondrosarcoma requiring differential diagnosis from metastatic tumor. Asian Cardiovascular & Thoracic Annals 2017; 25: 154-6.
4. Robert J, Akashdeep S, Rupinder K. "Ring and arc" calcification in a rib mass. Lung India 2012; 29:85-6
5. Bacha D, Ayadi-Kaddour A, Fenniche S, Marghli A, Kilani T, El Mezni F. Costal chondrosarcoma. Report of five cases. Orthopaedics & Traumatology: Surgery & Research 2009; 95:164-9.
6. Ohata, K., Chen, F., & Date, H. (2011). Rib chondrosarcoma with intramedullary progression completely resected by magnetic resonance imaging: Useful short inversion time inversion recovery sequence. Interactive Cardiovascular and Thoracic Surgery, 12(5), 853-4.
7. Roos, E., Van Coevorden, F., Verhoef, C., Wouters, M., Kroon, W., Hogendoorn, H., & Van Houdt, (2016). Prognosis of Primary and Recurrent Chondrosarcoma of the Rib. Annals of Surgical Oncology, *23*(3), 811-7.

Case Report

Case of benign familial fleck retina with foveal involvement

James Vassallo

Abstract

Retinal dystrophies constitute a diagnostic challenge in view of their rarity, wide range, and overlapping features, usually requiring multimodal investigations to establish the diagnosis. It is important to assess the inheritance pattern, and provide the patient with prognostic information. Treatment is limited.

Keywords

retinal dystrophy; flecks; drusen

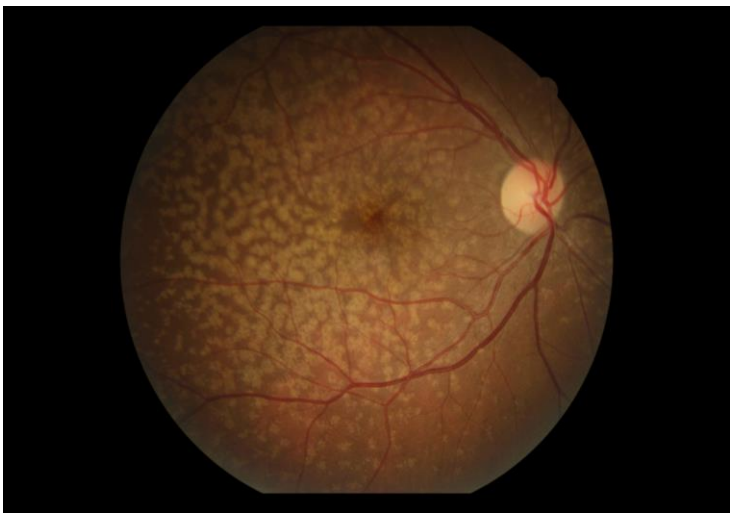
Case

A 37-year-old female presented for a routine eye test. She was asymptomatic. Fundoscopy revealed bilateral symmetrical widespread subretinal deposits, as shown in the colour photos.

Discussion

A provisional diagnosis of benign familial fleck retina was made based on the characteristic appearance described elsewhere.[1] It is usually autosomal recessive, but autosomal dominant inheritance has also been reported. It is the only case known in Malta, however retinal screening of family members of proband was not carried out. The patient will be observed and no deterioration in vision is expected. The fovea is usually not involved in this condition, so this case is atypical. Despite the presence of foveal flecks, the patient was asymptomatic, typical of this condition. Retinal flecks may be misdiagnosed as drusen or exudates, and are found in several fundus dystrophies. Pattern recognition is the primary method of establishing a diagnosis of benign familial fleck retina.

Figure 1: *Fleck retina, right eye*



James Vassallo MD(Melit) MRCSEd FICO FEBO
Department of Ophthalmology
Mater Dei Hospital
Msida, Malta
jamesvassallo2000@yahoo.com

Figure : *Fleck retina, left eye*

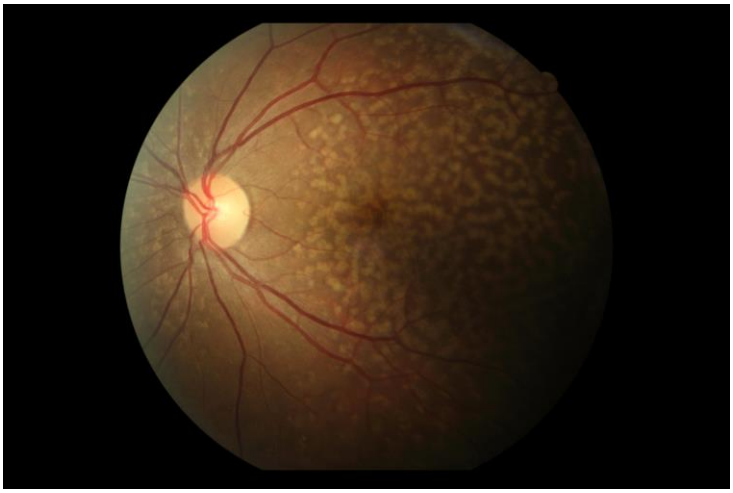


Image description

A multitude of yellowish, granular, ill-defined subretinal lesions in a mosaic pattern, mostly confluent, and some separated by normal retina. The macula, including the fovea, was heavily involved, but the peripapillary area was relatively clear. The extramacular area to the periphery was also similarly involved, but the lesions were smaller and more widely separated. The retinal vessels and disc are normal.

Reference

1. Dorairaj SK, Murthy KR, Ritch R. Four-generation familial benign fleck retina. Retin Cases Brief Rep 2007;1(1):25-6

Littoral Cell Angioma of the Spleen: a case report

Gabriella Grech, Angela Sultana

Abstract

The patient is a 54 year old, presenting with a 4 month history of worsening lower back pain, radiating to both lower limbs. CT Thorax Abdomen and Pelvis was carried out which showed a 6.2cm dense fluid density lesion in the spleen. The case was discussed at the multidisciplinary team meeting and open splenectomy was carried out. Histological diagnosis was consistent with an infarcted littoral cell angioma.

Gabriella Grech MD, MRSCEd*****
Department of Surgery,
Mater Dei Hospital,
Msida, Malta
gabriella.grech@gov.mt

Angela Sultana MD, FRCS (EDIN)
Department of Surgery,
Mater Dei Hospital,
Msida, Malta

**Corresponding author*

Key words:
Littoral cell angioma, benign, spleen, splenectomy, histology

Littoral cell angioma is a rare vascular tumour unique to the spleen, originating from cells lining the venous sinuses of the normal spleen.[1] It was first described by Falk et al. in 1991.[2] The majority of cases have been composed of multiple nodules of varying sizes in the spleen, benign and asymptomatic in nature.[3]

Case Report:

The patient is a 54 year old female, presenting with a 4 month history of worsening lower back pain, radiating to both lower limbs. The pain was associated with parasthesia, weight loss and loss of appetite. She was noted to have a high white cell count and C-reactive protein.

A Computerised Tomography (CT) Scan of the Thorax, Abdomen and Pelvis was carried out which showed a 6.2cm dense fluid density lesion in the spleen. This demonstrated peripheral enhancement with internal septations. There was no intraperitoneal rupture. The splenic capsule was intact and there was no subcapuslar extension. No further splenic lesions noted. The main differential diagnoses were splenic abscess, hydatid cyst and neoplastic tumour.

The CT Scan also showed bilateral sternoclavicular joint erosion with osteitis, multiple endplate sclerotic foci and bilateral sacroilitis. These findings explained the symptoms that the patient presented with. She was diagnosed with SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis) and referred to rheumatology.

Ultrasonography of the splenic lesion revealed a heterogenous lesion with a well-defined wall, internal septations and cystic areas, in keeping with an abscess. The patient was started on intravenous antibiotics and an ultrasound-guided drainage of the abscess was carried out. A sample of pus was sent

for microscopy, culture and sensitivity. Microscopy showed few polymorphs and no bacteria were seen or cultivated. The case was discussed at the multidisciplinary team meeting and open splenectomy was planned for the patient for definite diagnosis of the splenic lesion.

Histology showed a spleen measuring 100mm X 78mm x 75mm. On sectioning there was a well circumscribed lesion measuring 50mm in maximum dimension. The lesion was partly cystic and partly solid. The cystic component contained garish, yellow viscous material and solid component had a pale yellow cut surface.

On microscopic examination, the lesion consisted of abundant necrosis, acute and chronic inflammatory cells. Admixed amongst the necrotic debris and most prominent at the interface between viable splenic tissue and the necrotic area were plump vaculated histiocyte like cells, containing eosinophilic material. The background spleen appeared unremarkable. The cells were highlighted by CD68, CD31 and are negative for CD34 (different pattern of staining which highlights vessels). Stains for MNF116, CD1a were negative. S100 probably highlighted endogenous activated macrophages. Special stains for iron, fungal organisms and acid fast bacilli were negative. Diagnosis was consistent with an infarcted littoral cell angioma.

Literature review:

This tumour occurs mostly in middle-aged men and women and has equal sex distribution.[1] Several studies have shown associations of littoral cell angioma of the spleen with immunological or congenital disorders such as Crohn's disease, Wiskott-Aldrich syndrome, Epstein syndrome, lymphocytic colitis, ankylosing spondylitis, Gaucher's disease, myelodysplastic syndrome, chronic glomerulonephritis or aplastic anaemia.[4] Moreover, one-third of cases are associated with tumours of visceral organs such as colorectal, renal, hepatocellular, lung and pancreatic adenocarcinoma and therefore close clinical follow-up of these patients is recommended.[5]

Differential diagnosis of multinodular splenomegaly includes multiple haemangiomas, lymphangioma, hamartoma, haemangiopericytoma, hemangioendothelioma, angiosarcoma, lymphoma, metastatic disease, Kaposi's sarcoma and disseminated infections caused by fungi, mycobacteria, pneumocystis carinii and sarcoidosis.[6]

Radiological findings are rarely sufficient for making a definite diagnosis of littoral cell angioma of the spleen.[7] On ultrasound examination, the appearance of these tumours is variable. It includes mottled ecotexture without discrete lesions as well as isoechoic, hypoechoic and hyperechoic lesions.[8] On abdominal CT Scans, littoral cell angioma typically manifests as multiple hypoattenuating elsions that enhance homogeneously or inhomogeneously as these are vascular tumours.[9] On Magnetic Resonance Imaging (MRI), the nodular lesions of littoral cell angioma typically appears markedly hypointense with both T1 and T2 weighted pulse sequences. This reflects the presence of haemosiderin in the lesions due to the haemophagocytic capacity of the neoplastic cells.[3] The gold standard treatment is splenectomy. Reports of other treatements including glucocorticoids and angioembolisation have been published.[1] The definitive diagnosis is made on histology and confirmed with immunohistochemistry. There is a mixture of papillary and cystic areas. Neoplastic cells derived from normal splenic lining-littoral cells form the lining of these papillary and cystic areas.[10] This neoplasm has features of both endothelial and histiocytic differentiation with the typical and characteristic immunohistochemical pattern of littoral cell angioma being CD31, CD68, CD163, CD21, FVIII antigen positive; CD34, CD8 negative.[7,10]

Littoral cell angioma is a benign tumour of the spleen, which may be associated with malignancy, immunological and congenital disorders. The treatment of choice is splenectomy. The imaging features of many other splenic neoplasms may mimic those of littoral cell angioma but in such cases diagnostic signs and symptoms are usually present. In cases of incidental finding of splenic mass on imaging and the patient has no associated signs or symptoms, littoral cell angioma should be suspected.

References:

1. Chourmouzi D, Psoma E, Drevelegas A. Littoral cell angioma, a rare cause of long standing anaemia: a case report. *Cases Journal.* 2009; 2: 9115.
2. Falk S, Stutte H, Frizzera G. Littoral Cell Angioma. *The American Journal of Surgical Pathology.* 1991; 15: 1023-33.
3. Abbott R, Levy A, Aguilera N, Gorospe L, Thompson W. From the Archives of the AFIP. *RadioGraphics*. 2004; 24: 1137-63.
4. Bi C, Jiang L, Li Z, Liu W. Littoral cell angioma of spleen: A clinicopathologic study of 17 cases. *AJR Am J Roentogenol*. 2007; 36: 239-43.
5. Cosme Á. Littoral-cell angioma of the spleen: A case report. *World Journal of Gastroenterology*. 2007; 13: 6603.
6. Johnson C, Goyal M, Kim B, Wasdahl D, Nazinitsky K. Littoral cell angioma. *Clinical Imaging*. 2007; 31: 27-31.
7. Ming Z, Hui M, Bin Y, Rana N. Case Report: Littoral cell angioma of spleen. *Indian Journal of Radiology and Imaging*. 2009; 19: 210.
8. Bhatt S, Simon R, Dogra V. Littoral Cell Angioma. *Journal of Ultrasound in Medicine*. 2007; 26: 539-52.
9. Tatli S, Cizginer S, Wieczorek T, Ashley S, Silverman S. Solitary Littoral Cell Angioma of the Spleen. *Journal of Computer Assisted Tomography*. 2008; 32: 772-5.
10. Colovic R, Suvajdzic N, Grubor N, Colovic N, Terzic T. Atipical immunophenotype in a littoral cell angioma. *Vojnosanitetski pregled.* 2009; 66: 63-5.