The Independent Medical Expert Group (IMEG) 5th Report

Report and recommendations on medical and scientific aspects of the Armed Forces Compensation Scheme

February 2020

Topic 8 - Recognised Diseases: Radiation and Ocular Melanoma

Key Points

1. For completeness, and despite its rarity and our being unaware of any claims under the AFCS, we include a short section on Ocular Melanoma (OM) as a recognised disease.

2. Literature scrutiny provided information on definition and epidemiology. There are two types of OM, the more common Uveal Melanoma (UM) arising from the iris, choroid, ciliary body and the much rarer conjunctival melanoma. Age standardised rate is 0.4-1.2 cases per 100,000 and OM occurs most commonly in Caucasians and presents in the sixth or seventh decade of life.

3. The review covers diagnosis, clinical management, treatments and prognosis. If UM metastasises, spread is mainly blood-borne to lung, bone or subcutaneous tissues. Spread may occur early or only 10 plus years after initial treatment. When the tumour spreads, survival is limited to about 10-15% at one year.

4. The aetiology of OM or its sub-types is unknown. Risk factors include age, sex, ethnicity, socio-economic group, smoking, light eyes, fair skin, poor tanning, ocular melanosis, dysplastic naevi, family history as well as certain mutations in the tumours.

5. A role for UVR has been investigated with conflicting results. The 2003 US Survivor Epidemiological and End Results (SEER) study found no population increase in OM over the period 1974-98 in contrast to the position with skin melanoma. International Agency for Research on Cancer (IARC) investigated the relation between OM site and sites deemed accessible by sun exposure. Two studies suggested that tumours occurred in areas exposed to sunlight but the third did not. In a further ten studies of different design, findings on the OM link with UVR exposure were inconsistent. Other studies suggest that personal factors such as light eyes, fair skin and burning easily were predictors.

6. We conclude that at present neither OM nor its sub-types can be accepted as recognised diseases in the AFCS. More research, which we will keep under routine review, is awaited. Where AFCS scheme members make a claim, the determination will be based on the individual case facts, including full occupational history, contemporary medical understanding of causation and progress, and the relevant legislation.

Introduction

1. IMEG has previously reviewed the evidence on causation and possible service causes, particularly ultraviolet radiation exposure, for skin tumours, including Cutaneous Malignant Melanoma (CMM) (1), and in this Fifth report there is a section on CMM in aircrew. We are unaware of any claims for ocular melanoma under the AFCS but for completeness this paper briefly considers ocular melanoma as a recognised disease in the armed forces population. Ahead of detailed consideration of the topic we have reproduced the introduction to Recognised Diseases first set out in the Second 2013 IMEG report.

Recognised Diseases

Ahead of the paper on Ocular Melanoma we have reproduced the introduction to Recognised Diseases included in the May 2013 IMEG Report.

1. Lord Boyce in his review of the AFCS raised the issue that while under the War Pensions Scheme the majority of medical discharge cases suffering from physical disorders receive entitlement to a war pension, this is not the case under the AFCS. This is a reflection of the different standards of proof required in the two schemes. The standard of proof in AFCS is "on the balance of probabilities" (or "more likely than not"), which is the standard of proof in both civil compensation and the statutory compensation scheme for civilian occupational injury and disease, the Industrial Injuries Scheme.

2. At its inception in 1917, the standard of proof used in the War Pensions Scheme was "on the balance of probabilities". This was changed in 1943, at the height of the Second World War, when for injuries and disorders arising in service, the burden of proof transferred to the MOD to demonstrate that a service cause was "beyond reasonable doubt" not the cause of the disease or injury. The change was introduced at this time because inadequate record-keeping was leading to large numbers of claimants unfairly not receiving compensation.

3. In his report, Lord Boyce proposed that the IMEG should develop a list of Recognised Diseases for the AFCS. By this he meant that IMEG should review the medical literature and receive evidence from experts to provide guidance about the circumstances when "on the balance of probabilities", a disease having onset in or around service was more likely than not to be attributable to service in the Armed Forces.

4. The normal burden of proof in civil compensation and other statutory compensation schemes such as the Industrial Injuries Disablement Benefit (IIDB) Scheme is "on the balance of probabilities". For claims under AFCS, this implies demonstrating that military service is more likely than not (more than 50:50) the predominant cause of the injury or disease in the individual case. In the Industrial Injuries Disablement Benefit Scheme, for those conditions where there is sufficient evidence that this level of proof is satisfied, the disease is 'prescribed', i.e. attributable in the individual case to the particular cause in relation to clearly- specified circumstances of exposure.

5. In the individual case, attribution is usually based on sufficient evidence to answer the questions:

- Does the particular agent or exposure cause the disease, at least in some circumstances?
- If so, were the circumstances of the individual case such that the agent or exposure is more likely than not to have been the cause of the disease?

6. Recognition of a particular agent as the cause of a disease, and attribution in the individual case, is most clear when the cause is specific to the disease, or nearly so, and the probability of causation is high. Such conditions are now relatively uncommon, but a relevant example is occupational asthma, where the primary cause is an agent inhaled at work. The majority of cases of occupational asthma are due to the development of an allergic reaction to the specific cause encountered in the workplace (e.g. flour in a bakery). Asthma develops after an initial symptom-free period of exposure and recurs on re- exposure to the specific cause, in concentrations which do not cause respiratory symptoms in others similarly exposed or previously in the affected individual. Inhalation testing with the specific agent will provoke an asthmatic reaction in the sensitised individual (but not in others not sensitised). Also, for many agents, evidence of a specific immunological reaction (i.e. specific IgE antibody) will be found. In principle the specific cause of asthma can be demonstrated in the individual case.

7. The majority of diseases, however, are not specific to a particular cause. A particular cause may increase the frequency of occurrence of a disease, which can have other recognised causes. As an example, lung cancer is well known to be caused by smoking cigarettes. More than 90% of cases in the general population occur in cigarette smokers. A smoker of 20 cigarettes a day during adult life will increase his or her chances of developing lung cancer by some twenty-fold. In the case of lung cancer in a smoker of 20 cigarettes a day for 40 years we can say with confidence that it is likely that the lung cancer is attributable to the smoking of cigarettes.

8. However, there are also other causes of lung cancer, such as asbestos and ionising radiation. When are we entitled to attribute lung cancer in an individual to asbestos exposure? The lung cancer caused by asbestos is indistinguishable from lung cancer from another cause, such as smoking, so it has no specific distinguishing features. We have to ask the question: in what circumstances would it be more likely than not that the lung cancer was caused by exposure to asbestos? As the individual case has no distinguishing (or specific) features, we have to look at populations of people exposed in their work to asbestos. Among these, are there any circumstances where the frequency of the disease has increased sufficiently to make it more likely than not in the individual case that the lung cancer would be unlikely to have occurred in the absence of occupational exposure to asbestos? The answer is that, among other circumstances, the frequency (or incidence) of lung cancer was more than doubled in asbestos textile workers, both smokers and non-smokers, who worked for 20 years or more in an asbestos textile factory. In these circumstances we can conclude it is more likely than not the lung cancer is attributable to asbestos.

9. Why is a greater than doubling in the frequency of the disease so critical in determining attribution to a particular cause? We can consider a hypothetical 100 men working in a particular occupation (figure 1). Among these 100 men, as in the general population, the number of new cases of a particular disease is 10 each year, i.e. no different

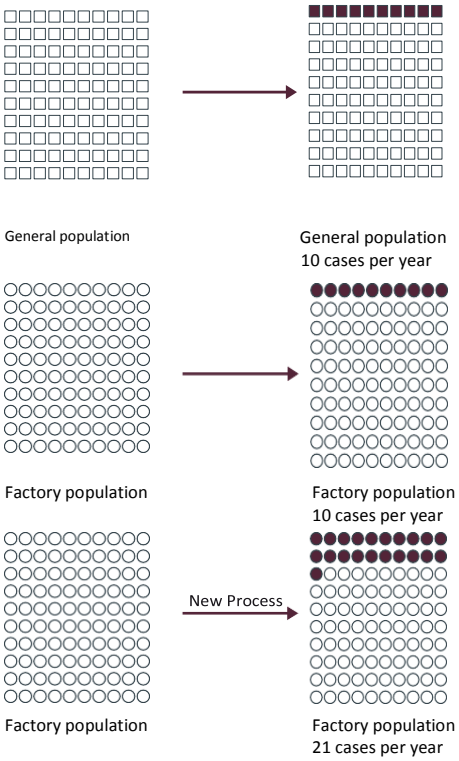

Fig 1. Increased incidence of disease from ten percent per year to 21 per year in factory population following the introduction of a new process

Sometime later, after the introduction of a new process, the number of cases of the disease in these 100 men increases to 21 each year, i.e. more than two times the previous frequency. We cannot distinguish the additional 11 cases from the 10 in whom the disease would otherwise have occurred. What we can say is that in any particular individual among the 21 cases, there is a more than 50:50 chance, or a greater than doubling of risk, that the disease would not have occurred without exposure to the particular cause. On the balance of probabilities, it is therefore more likely than not that the disease is attributable to the particular cause in the individual case. We can say that 'but for' his working in this factory it is unlikely the man would have developed the disease. The balance of probabilities has shifted to "more likely than not" and in this circumstance the disease can be attributed to the particular cause.

10. In the case of Recognised Diseases in the AFCS, we are therefore looking for evidence that service in the Armed Forces is consistently associated with an increase in the frequency of a particular disease or illness and whether there are circumstances where the frequency is more than doubled, making it more likely than not in the individual case that the disease was attributable to a cause in service.

11. It is also important to distinguish "all or none" diseases from "more or less" diseases. A well-recognised "all or none" physiological condition is pregnancy: one cannot be a bit pregnant. In contrast, many important conditions including high blood pressure, hearing loss and mental health disorders are "more or less" conditions. These have a continuum of frequency of symptoms without a clear distinction subject to expert opinion.

12. The epidemiological evidence informing these determinations should be of high quality, drawn from several independent studies and sufficiently consistent and robust that further research at a later date would be unlikely to overturn it.

Definition and Epidemiology

13. Ocular melanoma (OM) is the most common adult intraocular tumour. It is much less common than Cutaneous Melanoma (CMM), accounting for fewer than 5% total melanoma cases. There are two sub- types, Uveal Melanoma (UM) arising from the iris, choroid and ciliary body and, Conjunctival Melanoma (CM). UM accounts for over 85% of cases of OM, while CM constitutes an estimated 5% OM cases. OM is most common in Caucasians and then Hispanics, with age standardised rates of about 0.4-1.2 cases per 100,000 within Europe and usually presenting in the sixth or seventh decade of life (2). While overall rates of OM have been fairly steady over the last 35 years, in US Caucasians, the incidence rates of CM in males, as with CMM, appears to have been rising (3), and a Danish study showed an increase in rates of OM in Caucasian men of about 300% over the period 1943-1997 (4).

14. The uvea is made up of the iris, choroid and ciliary body. Some tumours are large and involve several parts of the uvea. True iris melanomas arise in, and are restricted to, the iris as opposed to spread from other structures and are distinct in their aetiology and prognosis, compared with the other UM types, collectively referred to as posterior uveal melanomas. Iris melanomas make up about 10% of total OM and usually have low grade histology, and a good prognosis. Benign pigmented iris lesions, iris freckles and naevi, are common in Caucasians occurring in 5-10% and rarely becoming malignant. These benign lesions provide no disabling effects. Iris melanomas are less likely to metastasize than choroidal melanomas and, if detected and treated early, are unlikely to lead to impaired vision. Like skin melanomas, iris melanomas may contain BRAF mutations classically associated with UV exposure (5).

15. Posterior uveal tumours, including malignant choroidal tumours, may also arise in benign pigmented lesions. They are not associated with BRAF mutations but, similar to blue naevi and ocular melanosis,

may contain GNAQ/GNA 11 or BAP1 mutations (6)(7). GNAQ and GNA 11 mutations occur early in tumorigenesis and do not predict prognosis (8), while BAP1 are strong predictors of metastatic spread and prognosis (9).

Diagnosis and Clinical Management

16. OM of all types usually presents as a visual problem or is detected as an incidental finding (2). Confirmation of diagnosis is usually by fundoscopic examination by an expert clinician followed, as clinically appropriate, by ancillary tests such as angiography, ultrasonography, tomography, autofluorescense and, for prognosis, cytogenetic analysis (10).

Treatment

17. Because OM is a rare tumour, meaningful randomised clinical trials evaluating treatment efficacy and effectiveness are limited and different interventions are often sponsored as best practice at different institutions. Especially for larger or symptomatic pigmented lesions, early detection and assessment of malignancy, followed by active treatment, are important in prevention of metastases, preservation of vision and disease survival. Since the 1980s, the current main treatment options are surgical or radiotherapy (RT), usually with charged particles or by brachytherapy. Newer less invasive protocols, including both surgical and RT and later chemotherapy, have been introduced, but in some cases have been reported as associated with subsequent visual loss and recurrence (11).

Prognosis

18. Uveal melanoma metastasizes in about half the patients by blood borne spread or local extension and in 80-90% cases spread is to the liver (13). Lung, bone and subcutaneous tissues may also be involved. When melanoma spreads, the current five-year survival rate is about 15% (14). Spread may develop early or late; i.e.10 or more years after treatment of the primary tumour (15). Current treatment of metastatic spread is limited with median survival, where there is liver involvement, of four or five months and a 1-year survival of 10-15% (16). Indicators of poor prognosis include older age, large tumour size, extra-scleral direct extension, ciliary body involvement and histological type (17).

Aetiology and Risk Factors

19. The aetiology of OM remains unknown. Published peer reviewed studies remain rare and are mainly case control in design with few longitudinal studies. Numerous risk factors, genetic and environmental have been identified or proposed but results are inconsistent (12). Work on causation of OM is hampered by its rarity and the different sub-types, the poor prognosis of OM, and so small study size. Studies do not always define caseness by objective criteria (eg histopathological confirmation) and issues such as suitable and adequately matched controls further limit studies. The sub-types of OM demonstrate different characteristics suggesting that different risk factors may apply. Suggested risk factors to date include age, sex, ethnicity, socioeconomic group, smoking cigarettes, light eyes, fair skin, poor tanning, ocular melanosis, dysplastic naevi, family history as well as the presence of certain mutations in the tumours.

20. The emerging understanding of a role for ultraviolet radiation in skin melanoma - cutaneous malignant melanoma, CMM - has led to expanded investigation of UVR and other radiation in OM. World Health Organisation (WHO) International Agency for Research on Cancer (IARC) Monograph

55, dated 1992 (18), and more recent update in 2012 (19) looked at solar and UVR radiation with commentary on the evidence of its connection to OM. It was noted that the 2003 study, based on US Survivor Epidemiological and End Results (SEER) data, found no increase in OM over the period 1974- 98 in contrast to the position on CMM (20). Three further studies examined by IARC, considered the distribution of choroidal melanomas in relation to ocular sites deemed accessible by sun exposure. Results in two studies suggested that tumours occurred in areas exposed to sunlight (21), (22) while the third, a much smaller study, found no preferential allocation of tumours related to likely sun penetration (23).

21. Nine case control studies and one cohort study reported on associations of sun exposure with OM. Four studies found increased risk for iris melanoma (IM) in people with light skin, eye or hair colour (24-27) and there was a link to outdoor activities in one of these (27). Four studies found an association between some measure of sun exposure and OM (26-29). In one (26) this was with sun exposure assessed by birth in a US southern latitude state compared with birth in a northern state. There was a further independent link of OM to dose of sun exposure based on duration of residence in the south or occupational exposure (26), (28). There were two meta-analyses. The 2005 meta-analysis of Shah
(30) included both case control and cohort studies and found no association with latitude of birth or outside leisure activity with OM, but weak evidence that the highest occupational exposures might increase OM risk; the relative risk was 1.4 (95% CI 0.9-1.5). The Weis 2006 meta- analysis (31) found strong evidence that having light eyes, fair skin and burning easily were associated with increased risk of OM. The IARC review also looked at artificial tanning, finding some evidence of a relation between that and OM, and where considered, an increased risk of OM with duration of use and use of artificial tanning from an early age (pre 20 years).

22. The IARC also considered occupation studies on cancer causation and the IARC report of 1990 focussed on welding (32). Six case control studies examined arc welding and OM, finding a positive association and dose response relationship based on job duration. In their evaluation of the two sets of reviews, IARC concluded there was: -

i) sufficient evidence in humans to accept the carcinogenicity of solar radiation and for a positive association between solar radiation and OM.

ii) sufficient evidence in humans to accept the carcinogenicity of UVR emitted from tanning devices including a dose associated causal association with OM.

iii) sufficient evidence to accept the carcinogenicity of welding and that current evidence establishes arc-welding as a cause of OM but with low risk and at present the underlying mechanisms are not clear; e.g. fumes, UVR or blue light

23. There have also been occupational studies on cooking and "working more than six months as a cook" has been proposed as a risk factor for OM. Again, the literature is restricted to small case control studies with often non-significant relative risk values. The first study to suggest a link had only two cases and six controls (33). Further, no possible basis for the link has been proposed or tested. The studies which have considered duration of employment as a cook have been conflicting (34) (35).

Conclusion:

24. Based on available evidence we cannot at this date recommend recognition of ocular melanoma (OM) or its sub-types, uveal melanoma (UM) and conjunctival melanoma (CM), as a recognised disease. More research, which we will keep under routine review, is awaited. Where AFCS scheme members make a

claim, the determination will be based on the individual case facts, including full occupational history, contemporary medical understanding of causation and progress, and the relevant legislation.

References:

1. MOD Fourth Independent Medical Expert Report Dec 2017. Available from https://www.gov. uk.government/publications/independent-medical-expert-report-2017.

2. Mahendra, J.K. et al. Ocular melanoma: when you have seen one, you have not seen them all: a clinical outcome study for the Survivor Epidemiological and End Results SEER database (1973-2012). Ophthalmol.2017; 11:153-160.

3. Yu, G. P.et al. Conjunctival melanoma: is it increasing in the US? Am. J. Ophthalmol. 2003; 135:800- 806.

4. Isoger, P.et al. Uveal and conjunctival malignant melanoma in Denmark 1943-1997. Ophthalmic Epidemiol. 32:29-32, 34:43-48.

5. Henriquez, F.et al. The T1799A BRAF mutation is present in iris melanoma. Invest. Ophthalmol. Vis. Sci. 2007;8(11):4897-900.

6. Van Raamsdank, C.D. et al. Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. Nature. 2009;457(7229):599-607.

7. Van Raamsdank, C.D. et al. Mutation in GNA11 in uveal melanoma. N. Eng. J. Med. 2010; 363(23):2191-2199.

8. Onken, M.D.et al. Oncogenic mutations in GNAQ occur early in uveal melanoma. Invest. Ophthal. Vis. Sci. 2008;49(12):5230-34.

9. Harbour, J.W. et al. Frequent mutation of BAP1 in metastasising uveal melanomas. Science. 2010; 330(6009):1410-13.

10. Pereira, P.R.et al. Current and emerging treatment options for uveal melanoma. Clin.Ophthalmol. 2013;7:1669-82.

11. Shields, C.L. et al. Primary transpupillary thermotherapy for small choroidal melanomas in 256 cases: outcomes and limitations. Ophthalmology. 2002; 109:225-234.

12. Krantz, B.A. et al. Uveal melanoma; epidemiology, aetiology and treatment of primary disease. Clin. Ophthalmol. 2017; 11:279-289.

13. Spagnolo, F.et al. Uveal melanoma. Cancer Treat.Rev. 2012; 38:549-53.

14. USA Eye Cancer Survival Rates. (2016) American Cancer Society.

15. Kolandjian, N.A. et al. Delayed system recurrence of uveal melanoma. Am. J. Clin. Onc. 2013; 36(5):443-9.

16. Singh, M. et al. Metastatic uveal melanoma.Ophthal.Clin.N.Am.2005; 18:143-150.

17. Augsburger, J.J. et al. Clinical prognostic factors in patients with posterior uveal malignant melanoma. Cancer.1990; 66(7):1596-600.

18. World Health Association International Agency for Research on Cancer IARC monograph on evaluation of cancerogenic risk in humans. vol 55 Solar and Ultraviolet radiation ISBN-13978-92-832- 11255-3 1992. Lyon France.

19. World Health Association International Agency for Research on Cancer IARC. monograph on the evaluation of cancer risk to humans. vol.100D Radiation Lyon, France. 2012.

20. Inskip, P.D.et al. Trends in the incidence of ocular melanoma in the United States,1974-98. Cancer Causes Control, 2003; 14:251-257.

21. Horn, E.P.et al. Sunlight and risk of uveal melanoma. J. Natl. Cancer. Inst. 1994; 86:1476-1478.

22. Li, W. et al. Patterns of tumour initiation in choroidal melanoma. Cancer. Res. 2000; 60:3757-3760.

23. Schwartz, L.H. et al. Lack of correlation between the location of choroidal melanoma and ultraviolet-radiation dose distribution. Radiat.Res.1997; 147:451-56.

24. Gallagher, R.P. et al. Risk factors for ocular melanoma: Western Canada Melanoma study. J Natl. Cancer Inst.1985; 74:775-778.

25. Holly, E.A. et al. Intraocular melanoma linked to occupations and chemical exposures. Epidemiology.1996; vol.7.no.1:55-61.

26. Seddon, J.M. et al. Host factors, uv radiation and risk of uveal melanoma. A case control study. Arch. Ophthalmol.1990 Sep.; 108(9):127-80.

27. Tucker, M.A. et al. Sunlight exposure as risk factor for intraocular melanoma. N. Eng. J. Med.1985; 313:789-92.

28. Hakansson, N.et al. Occupational sunlight exposure and cancer incidence among Swedish construction workers. Epidemiology. 2001; 12:552-557.

29. Vajdic, C.M. et al. Artificial ultraviolet radiation and ocular melanoma in Australia. Int. J. Cancer.2004 Dec.10; 112(5):896-900.

30. Shah, C.P.et al. Intermittent and chronic ultraviolet light exposure and uveal melanoma: a meta-analysis. Ophthalmology.2005 Sep; 112(9):1599-607.

31. Weis, E.et al. The association between host susceptibility factors and uveal melanoma: a meta-analysis. Arch. Ophthalmol. 2006.; 124:54-60.

32. World Health Association International Agency for Research on Cancer. IARC vol 49 A Review of human carcinogens. Chromium and nickel welding Lyon France 1990.

33. Guenel, P.et al. Occupational risk factors, ultraviolet radiation and ocular melanoma: a case control study in France. Cancer causes and control .2001. Jun; 12(5):451-9.

34. Stang, A.et al. Phenotypical characteristics, lifestyle, social class and uveal melanoma. Ophthalmic Epidemiol. 2003.Dec.; 10(5):293-302.

35. Schmidt-Pokrzywniak, A. et al. A case-control study: occupational cooking and the risk of uveal melanoma. 2010.BMC Ophthalmol.2010;10:26. Published online 2010 Oct.22: doi:10.1186/1471-2415- 10-26