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Title

What are the Red flags to aid the early detection of metastatic bone disease as a cause of back pain?

Laura Finucane- Corresponding author

HERE, MSK partnership

Fourth Floor

177 Preston Road

Brighton

BN1 6AG

Laura.finucane@nhs.net

447939104788

Susan Greenhalgh-Orthopaedics

Bolton Foundation Trust NHS

James Selfe

Department of Health Professions

Manchester Metropolitan University

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Background

Serious pathology as a cause of back pain has been described as rare, reported as 1% of patients presenting to primary care [1,2]. However, the prevalence of serious pathology is likely to increase as cancer survival rates improve [3]. Better medical treatment of primary cancers means patients are living longer putting them at greater risk of developing metastatic disease [4].

The second most common serious pathology to affect the spine after fracture, is metastatic bone disease (MBD) as a consequence of primary cancers [2]. The spine is one of the earliest sites affected especially in those with a history of breast and prostate cancer [4,5,6]. Metastases can affect any region of the spine: Cervical 20%; Thoracic 70%; Lumbar 20% [3]. The spread of MBD is not fully understood but its affinity to the spine is thought to be the result of hematogenous spread via venous or arterial routes. The complex spinal venous system, causes a slower venous flow allowing for deposits of tumour cells to occur and highly perfused vertebral bodies allow effective delivery of tumour cells [5,6].

The most common symptom of MBD is back pain, which is usually a benign condition with a prevalence of 80% in the general population. This makes it challenging for clinicians to differentially diagnose if the cause of a patient's back pain is serious pathology. It is critical therefore that any clinician faced with a patient with back pain screen for serious pathology first as missing or delayed diagnosis has significant consequences for a patient's prognosis including life expectancy, quality of life, medication tolerance and pain control [1,7,8].

Examples of red flags specifically related to cancer include night pain, weight loss and a past history of cancer [9]. Unfortunately the use of red flags is problematic as there is little or no high-quality evidence on their diagnostic accuracy with the exception of a past history of cancer [1,2]. The identification of serious pathology using a past history of cancer and back pain alone has been described as a blunt instrument if not used in conjunction with the type of cancer and the time since diagnosis [8]. For example, the risk of ovarian cancer spreading to bone is very small in comparison to breast cancer [10]. Equally, investigation of every person with back pain and a history of cancer would be extremely costly and detrimental to the patient, exposing them to unnecessary and potentially worrying investigations [10]. Clinicians are likely to use a combination of red flags to inform their suspicions of serious pathology. However, to date there is no evidence of the usefulness of red flags in combination and further work is needed to evaluate different combinations [1].

The red flags of night pain and weight loss used to detect serious pathology describe symptoms that potentially occur during the late stages of disease, yet the literature clearly states that early detection is critical for effective management and patient outcome [10,11,].

MBD can occur at any time with 50% occurring within the first 5 years after a primary diagnosis of cancer with some developing, 10 years and beyond [12,13]. This sometimes protracted timeframe makes it challenging for both patients and clinicians to associate symptoms with possible metastases. Once MBD has developed it is considered incurable with a life expectancy of just 2 years following diagnosis [6]. However, life expectancy could increase if essential treatment was administered in the

early stages when there is less disease burden and the patient is able to tolerate medication [14].

Early identification would also have an impact on quality of life and could reduce the burden of treatment on Health Services by managing the disease, and maintaining a patient's functional independence [11,15]. The consequences of untreated or late stage diagnosis can result in poor pain management and, in the worst case scenario, cause metastatic spinal cord compression [MSCC] which can lead to paralysis and compromise bladder, bowel and sexual function [16]. Further information on identification, diagnosis and management of MSCC can be found in Turnpenny et al [17] and NICE guidelines [18].

Currently it is unclear which red flags suggest the early presentation of MBD in the absence of cord compression. If red flags or clinical symptoms associated with early signs could be identified then clinicians would be able to ensure patients were managed appropriately in a timely manner resulting in better outcome. In addition, patients at risk could be informed of these symptoms so that they can act as their own advocates and present to an appropriate health care setting in a timely manner [19].

The following discussion focusses primarily on pain and night pain and then briefly discusses other symptoms of MBD.

Bone pain is the most common symptom associated with MBD [11,20,21]. The pain is most likely to be caused by the destruction of bone and the stretching of the periosteum as the tumour grows [22]. Bone pain has been described as having a gradual onset, intermittent, dull in character, becoming constant and increasing in intensity with time

[23]. Pain is prevalent in the early stages of MBD with 70% of patients describing pain associated with the disease [4]. Three distinct types of MBD pain are described; [a] local pain, which patients describe as a persistent gnawing, aching pain; [b] mechanical pain, which is aggravated by movement and [c] radicular pain described as sharp shooting, stabbing and burning [3,5,16]. Ju et al [5] state the importance of understanding the type of pain a patient experiences as this may help to give clues to its etiology. However, these descriptors are not helpful in differentiating between those patients who have MBD and those who have benign back pain as they are common descriptors used by both groups.

A further type of pain referred to as 'Incidence pain', is described as severe, unpredictable and intermittent occurring suddenly related to movement with several episodes through the day [23]. However this type of presentation is usually prevalent in the late stages of the disease [24].

Band like trunk pain has been identified by a number of authors as a sign of MBD. Greenhalgh and Selfe [25] suggest that band like trunk pain could be an early sign of serious pathology with patients often reporting this initially as a vague symptom. Scuibba and Goksalan [3] refer to band like trunk pain as a feature of those who already have MSCC. Turnpenny et al [17] concur and also link this symptom with signs of MSCC. Thus there is no consensus on whether band-like trunk pain is more likely to occur in the early or late stages of MBD, however it seems clear that clinicians should take the report of band-like trunk pain seriously.

Several authors [3, 11, 22, 26] report that bone pain at night is the most 'ominous' sign in patients with MBD. Night pain is a red flag associated with serious pathology but it

is also a common finding in benign back pain and this challenges its usefulness as a sign of serious pathology [27]. 'Ominous' night pain signs and symptoms are those that are aggravated rather than relieved by lying [18]. The patient often describes the need to get up and walk to ease the pain during the night or that they are unable to sleep lying flat and routinely sleep upright in a chair. It is often night pain that drives a patient to seek help and present to emergency departments [28]. Interestingly this may not raise alarm bells in staff working in emergency departments as staff routinely working at night may not see the significance of the patients 'night pain'.

Greenhalgh and Selfe [25] identified 'vague lower limb symptoms' and 'decreased mobility' as symptoms associated with the early signs of serious pathology. These symptoms have gone on to be used to identify the early signs of MSCC [10,17] but as yet they have not been specifically validated as early signs of MBD. As the disease progresses other clinical features manifest themselves with the second most common complaint being motor dysfunction followed by sensory dysfunction [3,5]. Systemic features may also become more apparent in particular the symptoms related to hypercalcemia which, are often vague and nonspecific and include fatigue, anorexia and constipation [20,21].

Pain is an early sign of MBD but probably not a very useful early red flag as it mimics pain described by those with benign back pain. It is not until the disease progresses that it becomes easier to describe, becoming constant, unrelated to mechanical activity with increasing severity and worse at night [5,11,21]. However, patients with a past history of cancer reporting increasing or new symptoms are worthy of monitoring [5].

Clearly not all patients with a past history of cancer will go on to develop MBD. What is not clear is the relative risk of developing MBD. There is a huge variability in the percentages described in the literature of those who will go on to develop MBD [30-70%]. This variability is demonstrated by breast cancer where there are a number of subtypes and the risk is dependent on the type and the stage at presentation. For example a person diagnosed with Oestrogen Receptor Negative breast cancer is at greatest risk of developing MBD in the first 2 years of initial diagnosis whereas Oestrogen Receptor Positive breast cancer is likely to relapse many years later [13,29]. However, these figures are constantly changing due to better systemic adjuvant therapies and earlier diagnosis but there remains a substantial risk of recurrence or development of MBD [5,29].

Knowing which patients are at greater risk of developing MBD maybe helpful when assessing a patient who presents with back pain and a past history of cancer. (see Table 1). Risk factors for patients with a history of breast cancer are related to the type of breast cancer, the size of the tumour on diagnosis and lymph node involvement [10]. Similarly patients with a history of prostate cancer are at greater risk of MBD if the size of the tumour is large, the prostate specific antigen [PSA] level is high at time of diagnosis [greater than 10 ng/ml], and they have a high Gleason score of 7 or more. The Gleason grading system evaluates the prognosis via a biopsy and the score determines the grade and how aggressive the cancer is.

Patients may not be able to recall the type of cancer they were diagnosed with but usually recall the type of treatment they received. Patients treated with radiotherapy and/or chemotherapy are more likely to have had an aggressive type of cancer and are therefore at greater risk [30].

Conclusion

Patients with a past history of cancer that has an affinity to bone such as lung, prostate and breast cancer, who present with new symptoms that persist should be thoroughly evaluated with a high suspicion of MBD [5].

Many authors emphasise the importance of recognising early symptoms of MBD [11,14] but no empirical studies describe what these early signs are. Whilst (back) pain is the single most reported presenting symptom, it is difficult to differentiate MBD pain from benign back pain in the early stages of disease. Following treatment for cancer it is very common for patients to worry that all aches and pains are linked to their previous cancer. This can make it difficult for both patients and clinicians to know what to be particularly concerned about [31]. It is not necessary to investigate all patients with a past history of cancer and back pain as not all patients will go on to develop MBD. Currently there are no national guidelines on recognising the signs and symptoms of MBD for healthcare professions [32]. A safety netting process of closely observing patients at risk over time is reasonable and an important consideration in effectively managing these potentially serious cases [20]. Using knowledge of a patient's risk of developing MBD and current red flags may help to raise a clinician's index of suspicion and result in timely investigation and management of the patient.

There is a gap in our knowledge with regards to the early signs and symptoms of MBD which have implications for further research. It is proposed that patients hold the key to defining early signs and symptoms of MBD and further research should involve the experience of patients living with the disease.

Laura Finucane

Table 1 Risk of bone metastases development (Oliver et al 2011)

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Edinburgh 2011 41:330-8.

Low Risk Tumours	High Risk Tumours
Tumours that rarely spread to bone, e.g. central nervous system malignancy or ovarian cancer	Tumours with a predilection for bony spread: prostate, breast, lung
Tumours with a low risk of secondary dissemination, e.g. patients treated for breast cancer who at diagnosis had grade 1 tumours of special type, such as 'tubular' and/or small tumours of around 1 cm in diameter or less	Patients treated for tumours of high grade and large size, which have shown evidence of a more malignant phenotype, such as local lymph node spread or lymphovascular invasion primary
Tumours' that cannot spread, e.g. premalignant conditions such as ductal carcinoma in situ of breast (DCIS)	

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