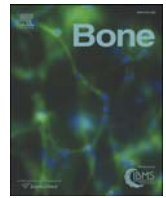




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## Review Article

## Circulating osteogenic precursor cells in non-hereditary heterotopic ossification

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## ABSTRACT

Non-hereditary heterotopic ossification (NHHO) may occur after musculoskeletal trauma, central nervous system (CNS) injury, or surgery. We previously described circulating osteogenic precursor (COP) cells as a bone marrow-derived type 1 collagen<sup>+</sup> CD45<sup>+</sup> subpopulation of mononuclear adherent cells that are able of producing extraskeletal ossification in a murine in vivo implantation assay. In the current study, we performed a tissue analysis of COP cells in NHHO secondary to defined conditions, including traumatic brain injury, spinal cord injury, cerebrovascular accident, trauma without neurologic injury, and joint arthroplasty. All bone specimens revealed the presence of COP cells at 2–14 cells per high power field. COP cells were localized to early fibroproliferative and neovascular lesions of NHHO with evidence for their circulatory status supported by their presence near blood vessels in examined lesions. This study provides the first systematic evaluation of COP cells as a contributory histopathological finding associated with multiple forms of NHHO. These data support that circulating, hematopoietic-derived cells with osteogenic potential can seed inflammatory sites, such as those subject to soft tissue injury, and due to their migratory nature, may likely be involved in seeding sites distant to CNS injury.

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## Contents

|                                                              |   |
|--------------------------------------------------------------|---|
| 1. Introduction . . . . .                                    | 0 |
| 2. Materials and methods . . . . .                           | 0 |
| 2.1. Patients . . . . .                                      | 0 |
| 2.2. Specimen retrieval . . . . .                            | 0 |
| 2.3. Tissue preparation and basic staining . . . . .         | 0 |
| 2.4. Immunofluorescence studies . . . . .                    | 0 |
| 2.5. Quantitation of COP cells in tissue specimens . . . . . | 0 |
| 3. Results . . . . .                                         | 0 |
| 3.1. COP cells are present in lesions of NHHO . . . . .      | 0 |
| 3.2. COP cells are found in early stage lesions . . . . .    | 0 |
| 4. Discussion . . . . .                                      | 0 |
| 5. Conclusions . . . . .                                     | 0 |
| Conflict of interest . . . . .                               | 0 |
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| Authors' roles . . . . .                                     | 0 |
| References . . . . .                                         | 0 |

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**Table 1**  
COP cells in early stage NHHO lesions.

| Diagnosis    | Age | Sex | COP cells per HPF (%) | Stage of lesion    |
|--------------|-----|-----|-----------------------|--------------------|
| TBI          | 36  | M   | 2                     | Fibroproliferative |
|              | 40  | M   | 7                     | Fibroproliferative |
|              | 53  | M   | 6                     | Fibroproliferative |
| SCI          | 25  | M   | 4                     | Fibroproliferative |
|              | 42  | M   | 8                     | Neovascular        |
| Trauma       | 21  | M   | 6                     | Fibroproliferative |
|              | 30  | M   | 3                     | Fibroproliferative |
|              | 38  | M   | 14                    | Fibroproliferative |
|              | 53  | M   | 2                     | Fibroproliferative |
| Arthroplasty | 52  | M   | 5                     | Neovascular        |
|              | 80  | F   | 6                     | Fibroproliferative |
|              | 84  | F   | 2                     | Fibroproliferative |
| CVA          | 44  | F   | 7                     | Neovascular        |

HPF, high power field; TBI, traumatic brain injury; SCI, spinal cord injury; CVA, cerebrovascular accident.

## 1. Introduction

Non-hereditary heterotopic ossification (NHHO) is the formation of mature bone in non-skeletal tissue, due to multiple injury types. Injuries to the central nervous, musculoskeletal, cutaneous, and cardiovascular systems have been associated with NHHO [1,2]. NHHO may be a clinically severe complication of pelvic and acetabular fractures, as well as following spinal cord, traumatic brain, and other non-neurological injuries.

Newly formed bone can lead to significant loss of motion at susceptible joints or contribute to stenosis in affected heart valves [1,2].

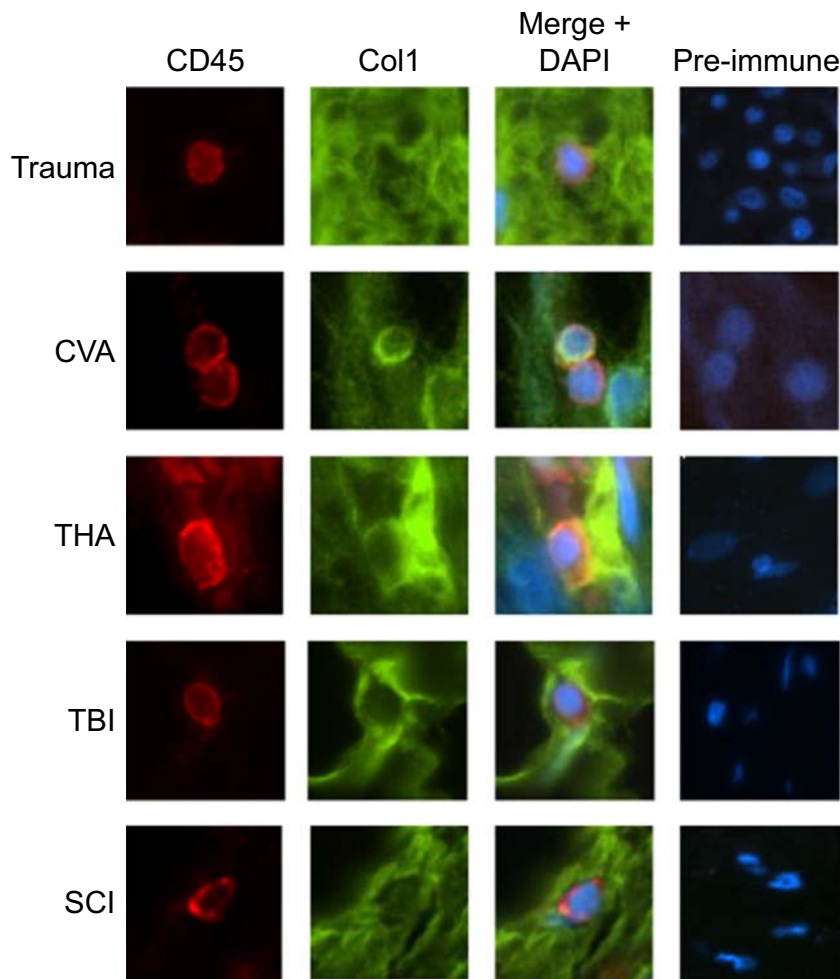
We previously described circulating osteogenic precursor (COP) cells as a bone marrow-derived type 1 collagen (Col1)<sup>+</sup>CD45<sup>+</sup> subpopulation of mononuclear adherent cells that are able to produce extraskeletal ossification in a murine in vivo implantation assay [3]. COP cells are present in lesions associated with a rare genetic condition, fibrodysplasia ossificans progressiva (FOP), where inflammatory swellings give rise to areas of HO [3]. They are also present in affected heart valve leaflets in end-stage aortic valve disease [4], where vascular injury and inflammation predispose tissue to calcification and ectopic bone formation. These observations suggest that COP cells may home to areas of injury and/or inflammatory and seed early lesions that undergo subsequent ossification.

It is unclear if COP cells are broadly associated with NHHO found in various clinical settings. We therefore undertook the current study to provide a systematic evaluation of COP cells as a contributory histopathological finding associated with multiple forms of NHHO.

## 2. Materials and methods

### 2.1. Patients

This study was approved by the Office of Regulatory Affairs institutional review board of the University of Pennsylvania. Thirteen patients underwent orthopaedic evaluation in the University of Pennsylvania



**Fig. 1.** COP cells are present in lesions of NHHO. Shown are COP cells expressing CD45 and type I collagen (Col1), detected in pre-osseous regions of the indicated NHHO lesions by in situ immunofluorescence. Original magnification is 400 $\times$ . Red, CD45; Green, Col1; Blue, DAPI. CVA, cerebral vascular accident; THA, total hip arthroplasty; TBI, traumatic brain injury; SCI, spinal cord injury. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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