The New England Journal of Medicine
Case Records of the Massachusetts General Hospital
“Continuing to learn from the patient…”

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Editor, Case Records of the MGH
Clinicopathologic Conferences (CPC’s): History

• 1870’s: Harvard Law School
  – Case method of teaching introduced by Christopher Langdell

• Walter B. Cannon, HMS
  – Found medical school lectures “a dreary and benumbing process”
  – Impressed by the enthusiasm of his roommate, a law student, for assigned cases
  – Introduced case based teaching at HMS in the 1890’s
  – 1900: Published “Case method of teaching systemic medicine” in the Boston Medical and Surgical Journal (later New England Journal of Medicine)

• Richard C. Cabot
  – Used cases as examination and teaching exercises at HMS
  – 1906: Published a monograph of case studies
The subtitle of the book stated his purpose: to teach “the differential diagnosis, prognosis, and treatment of actual cases of disease.”

Cabot was a renowned diagnostician; advocated careful patient histories and followup (not universally accepted at the time).
CPC’s: History

• 1908: Cabot joined staff of MGH
  – Realized his colleagues were unaware of potential of autopsy to clarify diagnoses
  – Together with James Homer Wright (Pathology), established Clinicopathologic Conferences
  – Published privately by MGH 1915-1923

• Published in Boston Medical and Surgical Journal (later New England Journal of Medicine) since 1923

• Popular conference emulated worldwide

• Editors at MGH
  – Richard C. Cabot (1923-1935)
  – Tracy B. Mallory (1935-1952)
  – Benjamin Castleman (1952-1974)
  – Nancy Lee Harris (2002-present)
  – Eric S. Rosenberg (2007-present)
Tracy B. Mallory
Chief of Pathology Service
Editor of Case Records
1935-1952
Editors of Case Records
Benjamin Castleman (1954-1974)
Robert E. Scully (1974-2001)
Evolution of the CPC’s during the 20th Century

- Cabot initially selected the cases and discussed them himself
- Later done as unknowns
  - Selected by pathologist, usually from cases autopsied at MGH
  - Cabot discussed without preparation
  - Lively participation of medical students, other physicians
- Initial diagnoses mainly based on autopsy
- Later, surgical biopsies became more common
- With subspecialization in medicine, other speakers were invited, conferences became more formal
CPC’s and NEJM - Mutual Benefit
Problems Facing the CPC’s in the 21st Century

• Cases became increasingly esoteric
• Difficult to find discussants
  – Interesting cases known to most MGH physicians
  – Production of a lengthy differential diagnosis daunting
  – Fear of “getting it wrong” in the NEJM
• Conferences poorly attended at MGH
  – Busy practitioners, competing conferences
  – Issues discussed not seen as relevant to practice
• NEJM dissatisfied with CPC’s
  – Reader survey: reduced interest, relevance to practice
  – Case histories and discussions overly long
  – Other types of case-based articles introduced
Is the CPC an Anachronism?

• At the turn of the last century
  – Focused on differential diagnosis, then the main activity of physicians.
  – Introduced the “new” diagnostic techniques of gross and microscopic anatomic pathology.

• At the turn of this century
  – Improved diagnostic techniques mean few cases are true diagnostic mysteries that can be solved.
  – Improved treatments create more options for management after diagnosis.
  – Physicians typically spend more time on management than on differential diagnosis.
  – CPC’s that focus on unusual differential diagnoses and rare diseases have limited practical value.
The CPC’s: Should they Continue?

• **Many issues need to be explained to practitioners:**
  – New diagnostic techniques
  – New prognostic and predictive factors
  – New treatments
  – New diseases

• **NEJM wants case-based exercises that benefit generalists and trainees.**

• **The patient mix and expertise of MGH and Harvard physicians can be an important resource for physicians and trainees.**

• **The CPC’s must adapt to modern medicine.**
The Updated CPC Mission

- Educate physicians in the diagnosis, classification, and treatment of disease, and in how to use new techniques for diagnosis and management, using “actual cases of disease”
  - The focus: practical - scientific advances that enhance understanding of disease in a way that impacts patient care.
  - The readers: medical students, practicing generalists, specialists
  - The forum: national and international

Harris NL. N Engl J Med 2003;348(22):2252
How do we do this?
Expand the format to include cases that illustrate issues in management

• Case history; brief discussion of differential diagnosis

• Radiology, Pathology:
  – new diagnostic techniques
  – new information about genetics or pathophysiology
  – pathologic features that predict prognosis or response to therapy

• Clinical discussant(s):
  – review management options and other issues
  – make recommendation for management

• Patient’s actual treatment and outcome are presented.
Diagnostic Mystery Cases: expand possibilities

• Include cases that are not zebras:
  – Common diagnostic problems that are still often missed
  – “A case where you SHOULD make the diagnosis!”

• Invite discussants who know the diagnosis
  – Physicians who actually cared for the patient
  – Describe their thought processes as the disease unfolded
  – Include both generalists and consultants “called in” to discuss specific aspects of the case

• Discuss both the differential diagnosis and management of the patient in the same case
  – Avoid the rigid “formula” that had taken over the CPC’s
Increase Clinical Relevance and Participation

- **Clinical Advisory Committees**
  - Each Department has a person or committee focused on CPC’s
  - Decide what issues are important to cover with appropriate cases
  - Identify cases and speakers

- **Move conferences to department rounds**
  - Reach a wider audience
  - Provide a forum for discussion
  - Chief residents involved in finding cases and speakers

- **Involve physicians in training**
  - House officers prepare case history and present at conference
  - Medical students on service present differential diagnosis or management recommendations
Changes in the CPC’s in the new millennium: Management cases

Figure 1

Karthikeyan, unpubl letter
Changes in the CPC’s in the new millennium: Authors per case

Figure 2

Average number of authors

Year

Karthikeyan et al unpubl letter
What makes a good case? Diagnostic problem

• Unusual presentations or complications of common diseases
• Typical presentations of uncommon diseases that practitioners should know about
• “New” diseases or categories
• A broad enough differential diagnosis to lead to an interesting discussion
• Sufficient clues to permit the correct diagnosis to be made
• A laboratory or other test that confirms the diagnosis
• Novel diagnostic techniques: radiologic, pathologic
What makes a good case?
Management problem

• Common problem with controversy on management
• Diseases with new data
  – Diagnostic, prognostic, predictive tests
  – New therapies
  – “New” diseases or categories
• Unusual problems that people should know about
• There should be an answer!
  – Sufficient data to permit an evidence-based approach to management of the patient
  – Sufficient followup to determine whether management was effective
What makes a good case?

• A hot topic!
  – A young adult dying from influenza
  – The first MGH WNV case
  – Burn victim from Rhode Island nightclub fire
  – Tsunami survivor treated by MGH physicians
  – A man impaled in a sculling accident
  – A man with respiratory failure due to 2009 pandemic H1N1 influenza virus
  – A case of wrong-site surgery
  – A young woman with gastrointestinal anthrax
  – A case of Listeriosis (during but not related to the U.S. outbreak)
  – A case of rabies in Massachusetts
“A 17 year-old Indonesian girl with hemiparesis after being swept up in a tsunami”
A man impaled in a rowing accident: Diagram of the Patient's Injury

A New Disease: TEMPII syndrome

A man with telangiectasias, erythrocytosis, elevated erythropoietin levels, monoclonal gammopathy, perinephric fluid collections, and intrapulmonary shunting
Case 23-2010: A 49-Year-Old Man with Erythrocytosis, Perinephric Fluid Collections, and Renal Failure

Hasan Bazari, M.D., Eyal C. Attar, M.D., Douglas M. Dahl, M.D., Raul N. Uppot, M.D., and Robert B. Colvin, M.D.

Presentation of Case

Dr. David B. Sykes (Hematology–Oncology): A 49-year-old man was admitted to this hospital because of erythrocytosis, perinephric collections of fluid, and acute renal failure.
Undiagnosed Medical Condition

- EPO = 4615 mIU/ml
  - (Normal 4-16)

- 0.79 g/dl IgG kappa M component

Massive perinephric fluid collections requiring intraperitoneal drainage

Pathological diagnosis: Renal lymphangieectasia
We request that any reader with thoughts about the diagnosis, further evaluation, or treatment contact Dr. David Sykes (dbsykes@partners.org) or any of the authors.
The TEMPI Syndrome — A Novel Multisystem Disease

• **T** = Telangiectasias
• **E** = Erythrocytosis & Elevated Erythropoietin
• **M** = Monoclonal Gammopathy
• **P** = Perinephric Fluid Collections
• **I** = Intrapulmonary Shunting
Telangiectasias
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
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</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
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<td>36</td>
<td>39</td>
<td>35</td>
<td>56</td>
<td>36</td>
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<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
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<tr>
<td>Geographic location</td>
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<td>Antwerp, Belgium</td>
<td>Los Angeles</td>
<td>Manchester, U.K.</td>
<td>Seattle</td>
<td>Indianapolis</td>
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<td>Race or ethnic group</td>
<td>White</td>
<td>Belgian</td>
<td>Indian</td>
<td>White</td>
<td>Finnish</td>
<td>Mexican</td>
</tr>
<tr>
<td>TEMPI syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Telangiectasias, most prominent over the face, trunk, arms, and hands</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
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<tr>
<td>Erythrocytosis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Hematocrit at presentation (%)</td>
<td>58</td>
<td>64</td>
<td>58</td>
<td>62</td>
<td>66</td>
<td>73</td>
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<tr>
<td>Erythropoietin (mU/ml)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>First measurement</td>
<td>16</td>
<td>50</td>
<td>600</td>
<td>NR</td>
<td>Increased</td>
<td>38</td>
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<tr>
<td>Highest value</td>
<td>&gt;5000</td>
<td>&gt;5000</td>
<td>&gt;5000</td>
<td>&gt;500</td>
<td>Increased</td>
<td>NR</td>
</tr>
<tr>
<td>Monoclonal gammopathy</td>
<td>IgG kappa</td>
<td>IgG kappa</td>
<td>IgG kappa</td>
<td>NR</td>
<td>IgG</td>
<td>NR</td>
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<tr>
<td>MGUS</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Perinephric fluid between the kidney and the renal capsule, without parenchymal renal cysts</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
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<tr>
<td>Requiring surgical marsupIALIZATION</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Intrapulmonary shunting, microscopic</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Hypoxemia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
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<td>Yes</td>
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<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Venous thrombosis†</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Spontaneous intracranial hemorrhage</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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# Seven Patients (Alive)

<table>
<thead>
<tr>
<th>Institution</th>
<th>M-protein</th>
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<tbody>
<tr>
<td>MGH</td>
<td>IgG-kappa</td>
</tr>
<tr>
<td>U. Antwerp, Belgium</td>
<td>IgG-kappa</td>
</tr>
<tr>
<td>USC, California</td>
<td>IgG-kappa</td>
</tr>
<tr>
<td>NIH</td>
<td>IgG-lambda</td>
</tr>
<tr>
<td>Mayo Clinic (Rochester)</td>
<td>IgG-kappa</td>
</tr>
<tr>
<td>St. Louis University</td>
<td>IgA-lambda</td>
</tr>
<tr>
<td>Paris, France</td>
<td>IgA-lambda</td>
</tr>
</tbody>
</table>
Complete and Partial Responses of the TEMPI Syndrome to Bortezomib

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Antwerp, Belgium

Casey O’Connell, M.D.
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Los Angeles, CA

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Perinephric Fluid
Serum Erythropoietin

![Graph showing Serum EPO levels over months with Velcade treatment highlighted.](image-url)
TEMPI: Treatment Response

<table>
<thead>
<tr>
<th>Institution</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>MGH</td>
<td>PR to bortezomib</td>
</tr>
<tr>
<td>U. Antwerp, Belgium</td>
<td>CR to bortezomib</td>
</tr>
<tr>
<td>USC, California</td>
<td>PR to bortezomib</td>
</tr>
<tr>
<td>NIH</td>
<td>PR to bortezomib</td>
</tr>
<tr>
<td>Mayo Clinic (Rochester)</td>
<td>On treatment (Cy-Bor-Dex)</td>
</tr>
<tr>
<td>St. Louis University</td>
<td>No insurance</td>
</tr>
<tr>
<td>Paris, France</td>
<td>Not on treatment</td>
</tr>
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</table>
TEMPI Syndrome

- Response to bortezomib suggest the paraprotein is causing the signs and symptoms of the disease.
- Efforts to identify the target of the paraprotein are ongoing.
The CPC’s: How do we do it?

• Finding cases:
  – Clinical advisory committee members identify topics and cases
  – Pathology residents and faculty suggest cases
  – Chief residents in clinical services suggest cases
  – Editor reviews preliminary autopsy reports, attends conferences where cases are discussed

• Organizing the conferences:
  – Discussions with Editor and clinical colleagues re topic, case, discussants, format
  – Associate editor prepares case history (protocol)
  – Two assistants help organize conferences, coordinate speakers
The CPC’s: How do we do it?

• Preparing the manuscript:
  – Discussants required to submit manuscripts, images, tables and references at the time of the conference
  – Conferences are taped
  – Editorial assistants transcribe proceedings, prepare rough manuscripts
  – Editor edits to NEJM specifications (length, focus, selecting images)

• Editors responsible for turning in publishable ms (40/year)
  – Electronically submitted via Manuscript Central
  – JMD reviews, requests edits (“too much like a review article! Focus on the patient!”)
  – Accepted ms goes to manuscript editing
  – Galleys, page proofs generate innumerable questions for all authors!
  – Letters to the editor…
CPC’s: Issues that Arise

• Do all the patients have to be seen at MGH?
  – Yes, but..

• Can patients or families attend the conferences?
  – Who decides?

• Do we need patient permission to discuss and publish the case? (HIPAA)
  – What if they say no?

• What about cases that illustrate problems in care or have a bad outcome?
  – Legal issues?

• Authors: financial conflicts of interest?
  – Can a discussant have financial ties to a company making a product used in the case?
The Case Challenge!

• Every other month, a case history is posted on the NEJM website 1 week before publication of the CPC.
• Readers are asked to vote on the correct diagnosis (multiple choice).
• Results of voting can be seen in real time on the web.
• Readers use the “comment” section to discuss their reasoning and choice of diagnostic test.
• 2 cases so far in 2013: >6000 readers voted!
  – Case 4-2013: A man with acute flank pain
  – Case 10-2013: A man with fever, arthralgia, and rash
The CPC’s in the Future

• Case-based teaching will continue to be important in medicine.
• Cases can focus on either differential diagnosis or management of disease - or both.
• Experienced physicians can demonstrate the application of modern medical advances to the care of an individual patient.
• The CPC’s can have an ongoing impact on the training of medical students and the practice of medicine around the world.
• What can we do to make them more interesting for you?